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Disease-a-Month

Chemoprophylaxis of Infectious Diseases (Part II)

MAXWELL FINLAND

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Chemoprophylaxis of Infectious Diseases

II. Other Applications in General Medical and Pediatric Practice

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Maxwell Finland

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Part I of this three-part series, which dealt with general considerations of chemoprophylaxis and its application to streptococcal infections, rheumatic fever, glomerulonephritis and bacterial endocarditis, appeared as the December 1959 issue.

Part III of Dr. Finland's discussion will deal with applications of chemoprophylaxis in surgical and obstetric practice. It will also have a general discussion and summary and will appear as the September 1960 issue.

INTRODUCTION

THE general problems involved in the applications of antibacterial agents, primarily sulfonamides and antibiotics, to the prevention of specific bacterial infections or of infectious complications that frequently accompany or follow other illnesses were discussed in a previous issue (1). The chemoprophylaxis of streptococcal infections, acute glomerulonephritis and bacterial endocarditis was also considered in detail. Although some generalizations and predictions concerning possible uses and probable effectiveness of chemoprophylaxis might be and have been ventured, these have not always stood the test of clinical and epidemiologic experience.

The practical application of chemoprophylaxis in various specific diseases depends on many factors, including the causative organisms of the infections which it is desired to prevent, some factors in the host, the drugs used, and particularly the specific conditions under which the drugs are given. Moreover, these conditions are subject to changes with changes in the ecology of various common pathogenic bacteria, their susceptibility to the drugs and their pathogenecity and opportunities to spread

following the extensive use of those drugs, as well as with the introduction of new antibacterial agents. The true picture of the value of chemoprophylaxis can therefore be obtained only from an evaluation of careful observations of its application in specific situations. The reliability of the data and of the conclusions based on such observations will then depend on the details with which the studies and controls were carried out, and they would then be applicable primarily to similar conditions and might not prove applicable or would at least have to be modified when applied to other conditions.

It therefore seemed best to summarize the results of some of the more relevant studies that have been reported for each of the various important diseases or situations in which prophylaxis has been used and for which objectively collected data are available. The present issue contains a review of such reports as they may concern medical and pediatric practice. A later issue will present the problems concerning the chemoprophylaxis of infections in surgical and obstetric practice and will contain a general discussion and summary.

MENINGOCOCCAL INFECTIONS

Epidemics of meningococcal infections in closed communities or among groups of people can be promptly and effectively halted and the organisms essentially eliminated by the mass prophylactic administration of sulfadiazine orally to all people within that community or group (2–4). This was clearly demonstrated during World War II in military installations in which there was a high incidence of carriers (inapparent or subclinical infections) and when increasing numbers of cases of meningitis were occurring. The carrier state could be effectively eliminated and the appearance of new cases of manifest infections halted by as little as 2 Gm. of sulfadiazine, although this amount given daily for 4 days produced the optimal effect. This type of mass prophylaxis has the advantage that it does not require identification of the individuals who are subclinically infected and can be accomplished essentially without side effects.

The brilliant success of this type of prophylaxis is due to the fortunate combination of the following factors: (1) Meningococci of all types are highly susceptible to the drug in vitro. (2) Resistant strains, if they occur, are extremely rare. (3) The brief course of treatment is highly effective in eliminating the

organisms from patient carriers. (4) There is no known reservoir of infection except in man. (5) The clinical disease probably begins with bacteremia, and in this situation the small numbers of circulating organisms are susceptible to low concentrations of the drug. (6) The brief course and small dosage required are associated with a minimum of minor untoward effects which make mass (and simultaneous) prophylaxis all the more feasible.

Similar prophylaxis is equally feasible and probably similarly effective among household and hospital contacts of infectious cases, although the actual need for and results of such prophylaxis have not been fully documented.

GONOCOCCAL INFECTIONS

It has been clearly shown that administration of a single tablet of 100,000 or 250,000 units of buffered penicillin G within 3 or 4 hours of exposure will protect most individuals from gonococcal infection resulting from that exposure; this has been accomplished with a minimum of reaction. It is also more acceptable than other forms of prophylaxis (5). This method was employed continuously and effectively in the United States Navy over a period of 3 years under conditions of normally high infection rates without evidence of occurrence of penicillin resistance and with a minimum of side effects, mostly minor in character (6). There was no indication that syphilis was suppressed by such treatment; the data even suggested that some cases of syphilis may have been prevented. In the Air Force, a similar program employing 500,000 units (2 tablets) after each exposure was associated with untoward reactions, mostly mild, in 0.18% of persons so treated, and occurring after less than 0.08% of such treatment (7). This type of prophylaxis is not recommended for general use, but only in areas of high prevalence of the disease.

Monthly injections of 2,400,000 units of benzathine penicillin G to prostitutes also appear to be effective in preventing the occurrence and spread of both gonorrhea and syphilis and are associated with very few untoward effects when given under proper medical supervision (8, 9).

Most of the data on the use of tablets of penicillin G were obtained several years ago. Penicillin V may now prove to be more effective because of its greater stability and better absorp-

tion. On the other hand, recent evidence of some decrease in the susceptibility of some strains of gonococci to penicillin and the increasing percentage of treatment failures from previously effective doses (10) raise the possibility that the low-dosage regimens may become less effective in preventing infection and that even increases in resistance may result from such usage. This may also be true of the prophylactic use of benzathine penicillin in prostitutes, as just mentioned, since low and possibly subeffective levels are maintained with such treatment during much of the interval between doses. Moreover, the increasing incidence of hypersensitivity to penicillin makes it likely that side reactions will be encountered more frequently and may be more serious unless proper precautions are taken to exclude allergic individuals and those with a history of such reactions.

Gonorrheal Ophthalmia of the Newborn

This infection has been effectively prevented by the proper use of penicillin (11–13). Intramuscular administration of 100,000 units or more of aqueous penicillin G to the mother before delivery or of 50,000 units to the infant immediately after birth and the application of about 7,000 units of penicillin G in ointment to the conjunctivae at the time of birth have all proved highly and equally effective. The ointment appears to be the most satisfactory, is at least as effective as silver nitrate and produces much less conjunctival irritation (13). Those who have applied penicillin ointment and studied its comparative effectiveness under controlled conditions are enthusiastic and prefer it. Although acknowledging the effectiveness of penicillin, others have not been willing to campaign for changes in the laws which, in many states, specify the use of silver nitrate as the legal method. This is also the most recent official view of the Committee on Medico-Legal Problems of the American Medical Association (14). The unfavorable effect of penicillin usage on the establishment and spread of antibiotic-resistant staphylococci in nurseries, as will be noted later, would seem to justify this position.

SYPHILIS

Unlike gonorrhea, which in ordinary conditions can be cured by a single moderate dose of any repository form of penicillin,

syphilis usually requires continuous treatment or maintenance of penicillin levels over several days and the use of much larger doses. This seems to be true also of prophylaxis. In the experimental syphilitic infection of rabbits, Hollander *et al.* (15) have shown that one or more subcurative doses of penicillin during the incubation period delay but do not prevent the syphilitic lesion, nor do they alter the usual course thereafter. This means that full therapeutic doses must be used in prophylaxis (8, 9) or in treatment of those who have had contacts with known infectious syphilis within 3 months. Plotke *et al.* (16) have shown that if such treatment is undertaken not more than 3 months after exposure to a freshly diagnosed case of infectious syphilis, 4% of treated contacts acquire syphilis, as compared with 25% among similar untreated individuals. Alexander and Schoch (17) reported that two thirds of such exposed and untreated individuals acquire the disease, while abortive treatment during the incubation period is almost 100% effective in contacts of infectious cases. King (18), on the other hand, opposes the use of abortive therapy after presumed risk-exposure, preferring to wait out the 3 months for the definitive diagnosis and treatment, except late in pregnancy or when dealing with backward peoples among whom adequate follow-up may not be possible.

Congenital Syphilis

A clearer and universally accepted indication for prophylaxis is in the prevention of congenital syphilis by adequate penicillin treatment of the infected or potentially infected mother during pregnancy (19, 20). Such treatment during pregnancy and any time before delivery is nearly 100% effective in preventing congenital syphilis in the child, provided there has been no relapse or reinfection of the mother between therapy and delivery.

OTHER TREPONEMAL DISEASES

There is evidence that the various pathogenic treponemes and closely related micro-organisms that cause such acute and chronic pathologic conditions as "endemic" (nonvenereally transmitted) syphilis, yaws, bejel and pinta in many parts of the world are all highly and more or less equally susceptible to penicillin. The development of long-acting repository forms of the antibiotic, such as penicillin in oil and aluminum mono-

stearate (PAM) and benzathine penicillin, has made possible campaigns of mass treatment of these diseases which have proved highly successful in reducing morbidity and sources of infection in several countries (21). In Haiti, after household contacts exposed to infectious yaws were treated with PAM, it was difficult to find a case of infectious yaws in the control areas where this method had been used. Similar experiences were accumulated in the endemic syphilis program in Yugoslavia. These surveys and mass treatment programs must include nearly the entire population and must be followed by similar periodic surveys and treatment at 6–12 month intervals for several years in order to insure a maximal eradicating effect by such a program (21).

BACILLARY DYSENTERY

Sulfonamides have for some time been used successfully in the treatment and prevention of bacillary dysentery. After several years of intensive study with absorbable and nonabsorbable sulfonamides, Hardy and Watt (22) noted that, during an outbreak, treatment limited to clinical cases did not reduce the incidence of the disease because of the large number of subclinical infections and carriers that were usually found. In military installations, treatment of all who had symptoms had no effect on the course of an epidemic. When patients and carriers were treated after a rapid bacteriologic survey, the incidence of infection was reduced but the disease was not eradicated. It was found necessary to treat, with small doses, *all* personnel in order to achieve a prompt and lasting decline in cases and carriers. Sulfadiazine has proved superior to the nonabsorbable sulfonamides (23, 24). Hardy (23) recommended, therefore, that when there is 10% illness, all members of the community or institution be treated with sulfadiazine, 1 Gm. twice a day for 7 days.

As early as 1945, however, sulfonamide-resistant strains were encountered in outbreaks (4). Flexner III strains were the first to be found resistant in the U.S. Navy, but subsequently other types, including Shigella sonnei, were found to be resistant. Streptomycin was first used in such resistant cases (25), but resistance to this antibiotic also developed rapidly (26). The broad-spectrum antibiotics, however, are active in vitro against all types and have been used successfully in treatment and control (26, 27). In general, chloramphenicol has been less active

than the tetracyclines; clinical and/or bacteriologic resistance to all of them has been encountered, and most frequently to chloramphenicol. Evidence suggests that small doses of the tetracycline (about one-fourth the normal dose) may be more effective than full doses in eradicating the organisms (28). This has been ascribed to a stimulating effect of the small doses on tissues, but may be due to the irritant effect of the larger doses on the gastrointestinal tract.

There are many possible reasons for the relatively disappointing results in the control and prevention of bacillary dysentery, as compared with the excellent results in meningococcal infections in which all patients and carriers are fairly promptly cleared of the organisms. (1) The organisms are much less susceptible and some species are more resistant than others, especially to the sulfonamides. (2) Resistant strains may appear and spread and not be affected by the antibacterial agents used. (3) The organisms in the intestinal lesion may be less accessible to the drug. (4) The organism may survive outside the body and provide reservoirs of exogenous infection and reinfection (4).

INFANTILE GASTROENTERITIS DUE TO ESCHERICHIA COLI

Gastroenteritis caused by certain specific serotypes of E. coli is a serious and highly contagious disease of infants under 1 year of age, particularly in nurseries for the newborn and in prematures, among whom it may be associated with high mortality and may be difficult to control. The causative organism is found in abundance in the feces, often in pure culture. Strains resistant to various antibacterial agents may appear and interfere with successful treatment and control of outbreaks (26, 29–32). In one hospital in which a large number of cases was encountered over several years, the organisms isolated during the first 8 months of 1953 were susceptible to sulfonamides and to many antibiotics, including streptomycin, chloramphenicol and the tetracyclines (31). After April, 1955, nearly all strains were resistant to all of these agents but sensitive to neomycin. After the latter had been used for about a year, 70% of new isolates were resistant to that antibiotic also. It was therefore felt that prophylaxis with antibiotics was not possible in that hospital.

Similar experience with the development of resistance to neo-

mycin was reported by others who shifted to the use of oxytetracycline and then observed the appearance of strains resistant to that agent (33). After the latter experience, nitrofurantoin was found to be effective and, at the time of the report, strains resistant to it had not appeared. However, when paromomycin (Hymycin, Humatin) was tried, it proved to be ineffective. This was not surprising because of the close relationship and complete cross-resistance with neomycin; the same could be predicted for kanamycin, which also is similar in activity and related in structure and shows complete cross-resistance with neomycin and paromomycin (34). Chloramphenicol and tetracycline are only suppressive and have only a limited effect in eradicating pathogenic E. coli (35). Although neomycin has been used successfully without the occurrence of resistance in some clinics (29), Stulberg *et al.* (36) observed bacteriologic relapses with sensitive organisms following the use of this antibiotic, often without recurrence of symptoms and after the organisms had apparently been eliminated. The latter workers could control an outbreak with neomycin only by the simultaneous treatment of all patients in the nursery. Polymyxin B given orally in doses of 10–25 mg. per kg. in 4 divided doses daily for 5 days eliminated the organisms, shortened the course of the disease and decreased the risk of reinfection.

With the appearance of a case of E. coli diarrhea in a nursery, it is important to treat promptly all children in that nursery. The susceptibility of the strain should be determined, although according to Cooke (37) it is probably wise to use a combination of neomycin and polymyxin orally in doses of 50 and 20 mg. per kg. per day, respectively, for about 5 days. Cultures should then be made at intervals to make sure that the organisms have been eliminated.

HEPATIC COMA

The clinical syndrome of hepatic coma or precoma (hepatocellular intoxication), which occurs in the late stages of cirrhosis or other destructive processes of the liver, is thought to be due to absorption of ammonium-containing substances from the bowel. It has been precipitated by administration of proteins, ammonium chloride, d-l methionine and chlorothiazide. Broad-spectrum antibiotics, notably chlortetracycline, which inhibit the growth of ammonia-producing coliform bacteria in the

gut have been successfully used in the prevention and treatment of this syndrome. Phear *et al.* (38), for example, were able to induce neurologic deterioration in 7 of 9 cirrhotic patients with "portal systemic encephalopathy" with methionine given orally. Oral administration of chlortetracycline prevented or delayed this deterioration. Chlortetracycline had some beneficial effect in rats with experimental liver failure (39, 40). The most effective agents have been neomycin and the related kanamycin and paromomycin (41–45). Their administration has also permitted a reasonable intake of proteins (42, 44) and the use of chlorothiazide without precipitating an attack (45). In a controlled study of 3 patients with impending coma associated with intestinal hemorrhage, neomycin proved to be superior to chlortetracycline and the combination of oxytetracycline and oleandomycin, and it permitted protein feeding (46). Interestingly, the favorable effect does not clearly correlate with the antibacterial effect, at least as revealed by ordinary fecal cultures (41). Doses of 4–12 Gm. a day have been used for long periods, continuously or intermittently; the larger doses are frequently accompanied by an increased number of soft stools or by frank diarrhea (43). This is the major untoward effect of such treatment.

Patients with liver failure are usually oliguric and potentially very susceptible to nephrotoxic agents. In such patients the usually small amounts of orally administered neomycin, or related drugs that are absorbed, may be retained and accumulate in the blood (47, 48). This may lead to further renal damage with increased nitrogen retention (47, 48) and also increase the possibility of serious auditory toxicity (48). Long-term oral therapy should be undertaken with caution in patients with severe impairment of renal function.

ACUTE RESPIRATORY INFECTIONS

It is well recognized that simple infections of the upper respiratory tract, including the common cold, are the most frequent antecedents and probably predisposing factors in acute bacterial pneumonia, and that some of the most serious and fatal ones complicate such viral respiratory infections as influenza and measles. Other local and systemic conditions also predispose to serious bacterial pneumonias. Since these pneumonias are usually due to susceptible organisms, it would seem logical to give

the antibacterial agents during the predisposing illness in an attempt to prevent these serious bacterial infections and their morbidity and mortality. Favorable effects may be expected from such prophylaxis only if (1) respiratory bacterial pathogens are present at the time of, or acquired during, the predisposing illness (2) they are susceptible to the drugs used, and (3) other less susceptible bacteria do not meanwhile establish themselves and produce disease which may then resist therapy with available drugs. An earlier review on antibacterial therapy in simple acute respiratory infections and influenza indicated that routine administration of sulfonamides and penicillin was effective only during high prevalence of streptococcal or other highly susceptible bacterial infections but did not favorably affect the incidence or clinical course of uncomplicated influenza or other common nonbacterial upper respiratory infections (49). Some of the more recent and relevant reports on the results of trials of chemoprophylaxis in various types of situations or illnesses predisposing to serious bacterial infections will be reviewed briefly.

General Use against Respiratory Infections

At the Great Lakes Naval Training Station, comparable groups of recruits were given, orally, 100,000 units of procaine penicillin, 250 mg. of chlortetracycline or a placebo daily during the first 6 weeks of training (50). Both penicillin and chlortetracycline prevented the occurrence of streptococcal infections but did not significantly alter the incidence or course of nonstreptococcal infections. Staphylococci resistant to penicillin and chlortetracycline were more frequently cultured from those receiving these drugs than from the controls, but there was no major change in the respiratory bacterial flora. Mild diarrhea occurred in some of those receiving chlortetracycline but subsided during continued treatment. At the same installation, Haight *et al.* (51) conducted a similar controlled study with oral penicillin, erythromycin and a placebo. The beneficial effects of penicillin and erythromycin on streptococcal infections were demonstrated, but these agents had no effect on other respiratory infections. Complications were not encountered, but it was concluded that the routine use of antibiotics is of no value and should be avoided.

Bacterial respiratory infections were prevented, whereas viral

infections were not, among children observed clinically in private practice during continuous administration of 200,000 units of benzathine penicillin orally twice a day or 600,000 units intramuscularly every 14 days for several weeks to over a year; there were some bacterial infections, however, during unprotected periods. The regimen was started during an outbreak of what probably were streptococcal infections, and it was felt that rheumatic fever, glomerulonephritis and febrile convulsions were prevented in the treated children (52). Among 402 other infants and children in private practice who were treated with potassium penicillin G orally for upper respiratory infections, "protection" was obtained, with only 0.5% minor urticarial reactions and no major complications of therapy (53).

In a better controlled study among children with uncomplicated viral and other respiratory tract infections of various etiologies, routine use of sulfonamides and antibiotics appeared to reduce the bacterial complications only among children under 4 years whose leukocyte counts were more than 10,000 per cu. mm., but apparently increased the complications among those with low or normal counts (54). The over-all incidence of complications was the same in treated and control groups. Symptomatic treatment was therefore recommended for those with negative physical findings and leukocyte counts below 10,000 per cu. mm. When blood counts are not available, treatment at the onset of the complication rather than at the onset of fever was recommended. In another study, 845 children in private practice with various viral respiratory illnesses, including measles and Asian influenza, were randomly selected for treatment with (1) full doses of tetracycline or a sulfonamide, (2) "prophylactic doses" of these drugs or (3) symptomatic treatment (55). No significant reduction in the occurrence of pneumonia, otitis media or other complications was noted in the drug-treated groups except those with a history of recurrent respiratory illnesses.

Measles

In 1942 Gibel and Litvak (56) reported the results of a study in which alternate children under 6 years old with measles but no bronchopneumonia at the time were given sulfathiazole routinely. The sulfonamide did not reduce the duration of fever, catarrh, otitis media or acute bronchitis; several cases of bron-

chopneumonia occurred during treatment but none among the controls. The drug was effective, however, in established cases of bronchopneumonia. In 1951, Karelitz *et al.* (57) claimed that the daily intramuscular administration of 300,000 units of procaine penicillin or of 50 mg. per kg. of chlortetracycline in divided doses, begun in the pre-eruptive or early eruptive stage of measles, resulted in the cure of complications already present and prevented further development of pulmonary, otitic or sinus complications. Temperature became normal 2 days earlier in treated children than in controls, but the rash, photophobia and cough were unaffected. The study was later repeated, using only 3 or 4 doses of procaine penicillin or a single dose of benzathine penicillin; none of the 114 patients receiving the former and only 2 of 61 treated with the latter developed bacterial complications during treatment, whereas about one fourth of 81 untreated patients developed complications, mostly bronchopneumonia (58). However, valid comparisons were not possible because 52 of the "treated cases" and none of the controls already had such complications when treatment was started. Similar cases were included in the more recent, so-called controlled study reported by Karelitz *et al.* (59) in which various antibiotics, but mostly penicillin or erythromycin, were used in patients observed either at home or in the hospital. Among patients observed at home, complications developed in 21% not given antibiotic therapy and in 16% of treated patients—in the latter mostly after the antibiotics had been discontinued. Among hospitalized patients only 8% of those treated and 44% of those not treated developed bacterial complications (59).

On the other hand, Weinstein (60), in an analysis of 428 patients hospitalized for measles, found bacterial complications on admission in 30% of 130 patients previously treated with antibiotics but in only 15% of the 298 who had not received such treatment. After admission, 78 were given antibiotics and 11 (14%) developed complications, as compared to only 4.6% among 350 (including 94 who had received antibiotics outside) not treated in the hospital. These findings suggested that antimicrobial agents do not prevent serious bacterial infections during measles and may actually be associated with an increased risk of their occurrence.

From a study of 4,728 cases of measles reported by members and associates of the College of General Practitioners (61) in Great Britain it was concluded that the routine administration of antibiotics was largely unnecessary; that sulfonamide drugs

had nothing to recommend them since they increased rather than decreased the complications, and that some of those with severe cases may have benefited from antibiotic therapy.

The Common Cold

Based on the concept which imparts to the common cold a property of enhancing the virulence of autogenous bacteria, Ritchie (62–64) in England advocates the use of autogenous vaccines and maintains that their use markedly reduces the incidence of colds and absences from work on account of colds. He also gives lozenges containing 15 mg. of 1 of the tetracyclines twice daily for 2 days at the first evidence of a cold and claims to have had favorable subjective results in all groups of individuals so treated, with a 90% drop in the development of full cold symptoms. The drugs used were chosen on the basis of sensitivity of the mouth flora (mostly Streptococcus viridans). For chronic cold sufferers he recommends repeated courses of vaccines. Ritchie's results are difficult to reconcile with the numerous negative and unfavorable results* of similar usages by others (65, 66), but it is of interest that Sulman (67) agrees with Ritchie and claims even better results from the use of chloramphenicol, which he prefers because bacterial resistance to it is rare. He gave the drug orally in a total dose of 3.5 Gm. in 5 days and maintains that 56 of 60 patients so treated could continue work, whereas in 38 of 40 given a placebo the progress of the cold was not altered. Lozenges of 15 mg. of chloramphenicol palmitate also suppressed the symptoms in 16 of 20 patients.

Influenza

Special interest was recently focused on this disease because of the serious and fatal complicating pneumonia frequently observed during the pandemic of Asian influenza and that previously encountered in other great pandemics. The recent fatalities were associated largely with infections due to antibiotic-resistant staphylococci, whereas complicating pneumococcal pneumonias, which varied in incidence in various localities, re-

*The most recent negative results in a controlled study of the use of bacterial vaccines for prevention of the common cold were reported from London and the Royal Air Force (180).

sponded to antibiotics in the usual way. The earlier studies indicating that antibacterial agents have no effect on the influenza viral disease (49) have been confirmed in cases of A′ influenza infection by Chancey and Meiklejohn (68) using penicillin or erythromycin and by Cronk and Naumann (69) using erythromycin. No bacterial complications were observed in either of these studies, even among controls, and mild gastrointestinal symptoms due to erythromycin were observed in both. In the latter study, 16% of those treated without erythromycin but none of those receiving the drug had a secondary rise in temperature on the fourth day.

Finke (70) gave prophylactic antibiotic therapy (penicillin V or tetracycline orally or penicillin plus streptomycin intramuscularly) to patients with chronic pulmonary disease as soon as they were suspected of having Asian influenza; most of the patients were already on continuous prophylactic antibiotic therapy. None of his patients developed severe infections, whereas their incidence was frequent in similar patients observed by others without such treatment. Such data are difficult to interpret for, although the complications of influenza that do occur may be severe (particularly in patients with chronic pulmonary disease), they are quite infrequent considering the wide prevalence of the uncomplicated disease. Moreover, other workers, who used penicillin, streptomycin and chloramphenicol as primary treatment in severe cases, observed severe superinfections with Staphylococcus aureus; they "gained the impression that the broad-spectrum antibiotics led to the development of an ecological vacuum in which the now ubiquitous staphylococcus became established" (71).

Large-scale cooperative studies under strict controls would be required to determine the efficacy of prophylactic treatment. The results would obviously depend on the choice of antimicrobial agents and their effectiveness against the prevalent respiratory pathogens, both those present at the onset and those acquired during the influenza.

Poliomyelitis

Some careful studies with bacteriologic control and clinical observations have been reported on the effects of antibiotics, used singly or in combinations, on the occurrence of respiratory infections in patients with bulbospinal poliomyelitis, particularly in those with severe cases requiring tracheotomy (72–74).

These studies showed clearly that, although recommended for routine use from the start by some authors (75), tracheal contamination was not prevented by the use of antibiotics locally or systemically and that the organisms recovered after several days of such treatment were predominantly Staph. aureus resistant to multiple drugs. The presence of these organisms was not always evidence of clinical infection, but when pulmonary infection did occur, such staphylococci and gram-negative bacilli were usually present; effective therapy then required appropriately selected chemotherapy and the mechanical removal of infected material from the trachea (74). Such infections were more common in those treated prophylactically than in untreated patients among whom pneumonia, when it did occur, was often due to susceptible pneumococci or hemolytic streptococci (72, 73). Lepper *et al.* (72), after intensive bacteriological studies, concluded that in spite of the possibility of preventing infections due to pneumococci, Hemophilus influenzae and streptococci, the unfavorable changes in flora during prophylaxis probably outweighed any good that might be accomplished; it is therefore preferable to follow the patient clinically and bacteriologically and give appropriately selected drugs only when the clinical condition warrants. Strictly observed isolation precautions appeared to be more important prophylaxis than antibiotic therapy.

Cardiac Failure

Because patients with chronic congestive heart failure tolerate respiratory infections poorly and in those with acute heart failure pneumonia is often a fatal complication, the prophylactic use of antibacterial agents may be considered of possible benefit in preventing such infections. McVay *et al.* (76) reported favorable results from continuous treatment with 0.5 Gm. of tetracycline in 2 doses daily for 20 months in a double-blind study of 149 patients with chronic congestive failure. The antibiotic-treated patients had significantly fewer respiratory infections and better appetite and subjective improvement than those who received a placebo. Strains of E. coli, Aerobacter, Proteus and Streptococcus faecalis of increased resistance to chlortetracycline were encountered in the treated patients but were not responsible for any illness. Only a few minor toxic effects, mostly pruritus and diarrhea, were encountered.

Another double-blind study of the value of prophylaxis with 2 Gm. of chloramphenicol daily for a week was carried out by Petersdorf and Merchant (77) among patients hospitalized with acute heart failure. In this study, fever was more frequent and lasted longer among placebo recipients, but the elevated leukocyte counts were not affected by the antibiotic. Pneumonia and death were somewhat more frequent among the chloramphenicol-treated patients. Among these, staphylococcal enterocolitis occurred in 2 and E. coli bacteremia, E. coli pyelonephritis and beta hemolytic streptococcal tonsillitis each occurred in 1 while receiving the antibiotic; in another, monilia was cultured from the pneumonic lung at autopsy. The authors concluded that antibiotics should not be used routinely in acute heart failure, but that special care should be taken to discover pulmonary infections early and to treat them promptly and vigorously with appropriately chosen antibacterial agents.

Unconscious Patients

Since pneumonia is a common immediate cause of death in comatose patients, Petersdorf *et al.* (78) studied the effect of routine administration of antibiotics in 32 unconscious patients who had no overt infection, using penicillin plus streptomycin or tetracycline, and also sulfisoxazole or nitrofurantoin in some; the results were compared with those in similar patients not given antimicrobial agents. The mortality was not affected, but pulmonary complications developed in nearly half of the prophylactically treated patients and in only 15% of the controls. Cutaneous staphylococcal infections occurred in 7 of the treated group and 2 others died of bacteremia due to gram-negative organisms; these complications did not occur among those from whom antimicrobials were withheld. Chemoprophylaxis did not reduce the staphylococcal carrier rates, and strains isolated from the treated group were more resistant than those from the controls. Prophylactic antibiotic therapy was therefore considered to be of no benefit and distinctly hazardous in unconscious patients.

Pertussis

Weinstein *et al.* (79) reported that treatment with the broad-spectrum antibiotics effectively eliminated Hemophilia pertussis

from the throat of patients with pertussis but did not affect the paroxysmal cough or reduce the secondary bacterial complications. They concluded that it was best to observe patients carefully and to treat complications only when they arose.

CHRONIC NONTUBERCULOUS RESPIRATORY INFECTIONS

Chronic bronchitis is a major cause of disability and of time lost from work in many places, particularly in Great Britain. Acute exacerbations usually occur during the winter months and follow simple acute upper respiratory infections. Bronchiectasis and emphysema are common sequelae in this condition and in bronchial asthma; these too are aggravated by simple upper respiratory infections. Hemophilus influenzae and pneumococci are the commonest pathogens during exacerbations. It is therefore not surprising that attempts have been made to prevent the acute exacerbations and minimize their effects by prophylactic use of antibiotics that are active against these organisms; several reports of controlled clinical trials, mostly in Britain, are available.

In Rochester, N. Y., Finke (80–82) has pursued various programs of continuous therapy in a group of children with persistent or recurrent bronchopulmonary disease, using an aerosol of penicillin, at first, and other antibiotics as they came along. In 1953 he reported excellent results in children under such treatment as compared with similar children who were not treated and maintained that progressive and permanent damage was thus prevented (80). He also recommended combined antibiotic-cortisone therapy continuously in children with "infectious asthma" and claimed to have prevented chronic disabling disease in early cases and to have rehabilitated patients with advanced cases by such treatment (81). He used penicillin V in both types of cases, and tetracycline during severe infections, with reduction in absence from school, increased vital capacity and absence of secondary bacterial infections. Side effects were not encountered with penicillin V and were minimal with tetracycline. He considered this a safe type of prophylaxis (82). Comparisons were based on findings in other groups of children, but there were no acceptable controls, so that these results are difficult to evaluate.

In a controlled study of the use of penicillin V, 120 mg. by

mouth 4 times daily during the winter months in asthmatic children, Lewis-Faning and Davies (83) could detect no favorable effect. They attempted to quantitate and compare the number of times the patients used inhalers; the number, duration and severity of asthmatic attacks; the amount of wheezing; school absenteeism, and the amount of sputum. They could make out no advantage in favor of the treated children over the controls.

McVay and Sprunt (84) conducted a double-blind study among adults with chronic bronchitis in Memphis, using prolonged treatment with chlortetracycline, 250 mg. twice daily. The antibiotic reduced the number of episodes of infection, the need for and duration of hospitalization and the erythrocyte sedimentation rates and increased the weight and hemoglobin content, while producing a minimum of side effects. Resistant gram-negative organisms appeared but did not constitute a problem.

At Brompton Hospital in London, oxytetracycline or tetracycline was given in doses of 250 or 500 mg. 2 or 3 times daily (according to tolerance) during the 6 winter months, and some of the same patients were studied during control periods without antibiotic (85, 86). About two thirds of the patients showed prompt, and often striking, improvement, but only a minority continued the treatment for more than 1½ years. Side effects, mainly diarrhea, occurred in about half of the patients and in some necessitated cessation of treatment. One fourth of the patients had resistant staphylococci in their sputum at the end of the trial.

A controlled trial of 6 months of continuous treatment with oxytetracycline, sulfonamides and H. influenzae vaccine in adult chronic bronchitis was conducted in Leeds (87). Patients receiving oxytetracycline showed considerable clinical improvement, and the effects were even better in those who took sulfonamides in addition, but a sulfonamide alone was of no value. The vaccine had no effect on the occurrence of H. influenzae in the sputum, had no beneficial effect clinically and was considered to have no place in the treatment. Hemophilus influenzae and pneumococci were the most frequent pathogens in the exacerbations, the former being more common in purulent than in mucoid sputum. There was no synergistic effect of the combined treatment on the bacterial flora. A longer follow-up of the patients treated with or without oxytetracycline indicated that treatment for 1 year or more not only prevented relapses but increased

the rate of improvement the longer the treatment was maintained (88). Since 80% of relapses occurred in the winter months (September through February), the authors recommended continuous treatment during these months to permit patients to maintain effective and useful employment.

A controlled trial of a sulfonamide (0.5 Gm. of sulfadimidine) 3 times daily conducted during 2 winters in cases of chronic bronchitis resulted in no fewer exacerbations than among patients receiving a placebo (89). On the other hand, sulfamethoxypyridazine, 0.5 Gm. daily, given through the winter to 12 patients reduced the number of flare-ups to 8 as compared with 34 among the same patients during the previous winter (90).

In Glasgow, Buchanan *et al.* (91) reported on a controlled comparison of the continuous use of tetracycline or a placebo given twice daily on an outpatient basis in similar cases of chronic bronchitis for periods up to a year. Tetracycline reduced the number of exacerbations that followed ordinary head colds. Here, too, H. influenzae was the most common pathogen; it persisted in spite of the antibiotic, although pneumococci were cleared. Resistant organisms did not emerge except for occasional staphylococci found at the end of the treatment period. Side effects were rare, and defaulters were more frequent among the controls than among those receiving tetracycline.

Another double-blind study in London was designed to determine the effect of vigorous oxytetracycline treatment of the acute attacks (92). The antibiotic or a placebo was given for one week, beginning at the onset of each exacerbation. Those on oxytetracycline lost about half as much time from work with each attack as did the placebo-treated controls, who in turn lost less time than those left untreated. The presence or absence of H. influenzae or pneumococci did not affect the length of the exacerbation, and no resistant organisms were encountered. The authors suggested that regular supervision and prompt treatment of exacerbations was also a useful method of management of chronic bronchitis.

A controlled comparison of the effects of prophylaxis with penicillin, oxytetracycline or a placebo in patients with severe bronchiectasis was conducted for the Medical Research Council in 12 centers, using 500 mg. 4 times daily 2 days each week for a year (93). Each group showed a reduction in the volume of sputum, but this was greatest and most rapid in those receiving oxytetracycline, who also had less cough, dyspnea and disability

and fewer episodes of fever and days in bed. There was no serious toxicity. From an economic point of view, although the oxytetracycline was the most effective, it was felt that the much greater cost did not warrant its preference over penicillin.

A double-blind trial of continuous administration of tetracycline, with or without oleandomycin, in chronic bronchitis was carried out for 2 years in Edinburgh (94). This led to the conclusions that, although expensive, tetracycline was less costly and more effective than treatment of exacerbation in the hospital and that its use offered a safe and reliable method of preventing such exacerbations. Side effects were mildly troublesome. There were no gross bacterial changes, but resistant coliforms and Staph. aureus appeared without causing trouble in the treated patients.

Another double-blind study of the effect of tetracycline, penicillin, an oleandomycin-penicillin mixture and a placebo given continuously for 3–22 months in patients with chronic bronchitis and bronchiectasis was reported from Chicago (95). Patients given tetracycline had fewer and shorter episodes of fever and illness than any of the others; the oleandomycin-penicillin mixture was slightly better than penicillin alone or the placebo, but penicillin alone was no better than the placebo. Pulmonary function and the volume of sputum were not significantly affected by any form of treatment. The presence of H. influenzae was usually associated with longer illness from lower respiratory infection. Tetracycline was the most effective in reducing the frequency with which this organism was isolated from sputum, but tetracycline-resistant staphylococci implanted more frequently than sensitive ones in the patients receiving this antibiotic.

A trial of continuous treatment with erythromycin for 12 weeks in patients with chronic obstructive pulmonary emphysema was reported from Seattle (96). Most of the patients considered themselves improved, but all actually showed mild deterioration in gross ventilatory measurements. Pneumococci disappeared, leaving Neisseria catarrhalis in the sputum. Intercurrent infections occurred with the same frequency as in matched controls, and no clinical differences were discernible.

The effects of continuous or intermittent treatment with penicillin V, tetracycline and a placebo given twice daily were studied in cases of chronic bronchitis under the auspices of the British Tuberculosis Association (97). Neither drug significantly reduced the number of exacerbations, but both of them

reduced to approximately one-half the number of days lost from work as compared with the placebo.

Pulmonary Mucoviscidosis (Cystic Fibrosis of the Pancreas)

In children with mucoviscidosis (pancreatic fibrosis), chronic and recurrent acute pulmonary infection is the most serious complication. At the Children's Hospital in Boston, continuous prophylaxis with a daily dose of one of the tetracycline antibiotics given on an outpatient basis has maintained such patients essentially free from serious relapses (98). Resistant staphylococci were frequently found but did not produce exacerbation in these children. Bruyn (99) noted that if treatment with chlortetracycline is started within 6 months of onset of symptoms, the subsequent course of children with mucoviscidosis is essentially similar to that of normal children. These findings were confirmed by Stowens (100), who also noted that chlortetracyclines increased the utilization of protein by such patients.

TUBERCULOSIS

Lambert (101) has recently reviewed the work reported on the chemoprophylaxis of experimental tuberculosis in small animals. Various doses of isoniazid have prevented tuberculosis during treatment. The fate of the animals after treatment is stopped depends on the period of treatment, the species of animal and other factors, but even guinea-pigs remain free from tuberculosis for many months. Immunity to subsequent challenge depends on the size of the infecting dose; when that is small, isoniazid interferes with immunity to subsequent challenge (102, 103). Bartmann (104) was able to cure minimally aerosol-infected calves and minimally infected guinea-pigs by continuous isoniazid administration in doses of 5–10 mg. per kg. per day. In monkeys, however, only 50% of exposed animals remained healthy in the post-treatment period. The significance of these observations for human infections is difficult to evaluate.

In 1954, Lincoln (105) called attention to the impressive effects of antimicrobial therapy on the prognosis in children with active primary tuberculosis at Bellevue Hospital, where the mortality was reduced progressively from 21.5 to 1.5%. In

the untreated children, 90% of the deaths occurred within the first year after the diagnosis was made, and in the great majority this was due to tuberculous meningitis. She therefore recommended that every child with active tuberculosis, as demonstrated by a positive tuberculin test, be treated with isoniazid, even though the roentgenogram is normal; treatment should continue for a year to cover the period when serious complications can be expected. Debré (106) endorsed this program and reported highly impressive results in a controlled study of treatment with full doses of isoniazid plus para-aminosalicylic acid given to positive tuberculin reactors who were known to have had negative reactions within the previous 6 months. A preliminary report of a strictly controlled cooperative study indicated that 4–6 mg. per kg. daily of isoniazid alone given for a year prevented 80% of serious complications as compared with similar children given a placebo (107). Drug toxicity was minimal.

Zorini (108) treated 600 tuberculin-positive, clinically and roentgenologically normal children, aged 4–11 years, from tuberculous families with increasing doses of isoniazid (10–20 mg. per kg. per day), half of them for 2 months and the others for 4 months. The children improved clinically and gained weight; toxicity was rarely encountered. In some it was necessary to repeat the course because of continuous exposure. Reactions to tuberculin increased, decreased or remained unchanged but did not become negative in any instance. Robinson *et al.* (109) reported, however, that isoniazid, 8 mg. per kg. daily, started in 4 children 2–24 months old when the Mantoux test in 1:1,000 was positive and the roentgenogram of the chest negative, reversed the tuberculin reaction to negative in 6 or 7 months.

Treatment of primary tuberculosis does not prevent the segmental atelectasis from pressure of hilar lymph nodes and bronchial perforations that may occur even after 12–14 months of therapy (110), but there is probably no increase in natural frequency in treated children (111, 112).

The procedure referred to above may be considered early therapy. A genuinely prophylactic study was carried out by Dormer *et al.* (113) in South Africa. They give isoniazid to 98 babies born of mothers with active tuberculosis, nearly all of whom helped care for the children and breast-fed them without any special precautions. There were no adverse effects in the babies or their mothers; only 7 of the children, 4 of whom did not get the full course, developed positive tuberculin reactions. The authors concluded that chemoprophylaxis completely pro-

tected the infants but provided no immunity, and they suggested the advisability of concomitant vaccination with isoniazid-resistant BCG.

On the basis of available data which she reviewed, Lambert (101) suggested the following indications for chemoprophylaxis:

DEFINITE INDICATIONS.—(1) Tuberculin-positive children under 3 years of age. (2) Tuberculin-negative children up to 3 or 5 years old exposed to continuous and unavoidable risk. Vaccination with isoniazid-resistant BCG would be desirable in such children. (3) Persons of any age in whom a positive tuberculin conversion is known to be a recent event.

POSSIBLE INDICATIONS.—(1) Short-term contacts with tuberculous patients, such as nurses or medical students working for brief periods on tuberculosis wards. (2) Patients on long-term therapy with corticosteroids. (Zorini [108] also included patients with pneumoconiosis or after gastrectomies or during severe respiratory infections, but it is felt that such patients might be considered only if they have evidence of healed tuberculosis.) (3) Accidental infection with tubercle bacilli: in this instance full doses and more than one drug should be used because the infecting dose may be a large one.

Lambert (101) also feels that chemoprophylaxis could well be used more widely in tuberculin-positive subjects in areas where the incidence of the disease is low. It is also to be emphasized that treatment of established tuberculosis in any individual is often partly or wholly prophylactic. In pleurisy with effusion, therapy may have very little effect on the immediate course but does prevent subsequent serious illness. An expert committee of the World Health Organization (114) also emphasized the importance of treating all pulmonary tuberculosis, even on an ambulatory or domiciliary basis where hospital facilities are inadequate, using isoniazid plus para-aminosalicylic acid if possible or otherwise isoniazid alone. The committee also recommended chemoprophylaxis with isoniazid alone for tuberculin reactors exposed to infectious tuberculosis patients.

STAPHYLOCOCCAL INFECTIONS IN NURSERIES

Considerable interest has been focused recently on staphylococcal infections in hospitals (115), much of it stimulated by the occurrence of such infections in newborn infants. These out-

breaks have been widespread in nurseries in many countries and associated with high morbidity and substantial mortality (116). They have added significance because they are always associated with the occurrence of breast abscesses in the mothers and give rise to a high incidence of staphylococcal infections in other members of the families after discharge from the hospital (117). For the most part, these outbreaks have been caused by staphylococci that are lysed by phages of the same types or patterns which always included 80 and/or 81 and sometimes 1 or more among types 42B, 47C, 44A, and 52 (116). Various methods have been suggested for coping with these outbreaks (115), most of them dealing with environmental factors; only those involving the use of antibacterial agents and which have been subjected to some controlled study will be mentioned here.

In England, considerable use has been made of detergents and antiseptics such as hexachlorophene in attempts to reduce cross-infection among newborn infants. Simpson *et al.* (118) found dusting of the umbilical stump and the front of the infant's abdomen effective for that purpose. Still better results were obtained by these authors when use of this antiseptic was begun in the delivery room and it was applied to the entire trunk. Routine application of this procedure greatly reduced the incidence of staphylococcal sepsis in the infants and their mothers (118).

Erythromycin was used successfully in the treatment of such infections by Forfar *et al.* (119). They treated all infected infants before discharge and considered this to be an important aspect; treatment was given for 2–9 (average 4) days without clinical failures. The additional use of streptomycin did not improve the results. However, in some of the cases conjunctivitis did not respond, and chloramphenicol ointment was used locally with greater success in such cases (120). They had success with continuous use of this method over 2½ years without encountering erythromycin-resistant staphylococci (121). Shaffer *et al.* (122, 123) also employed erythromycin successfully. They believe that control of the nursery epidemics depends on the prevention of colonization of the infants by the staphylococci rather than on mere isolation and quarantine, and that this is not accomplished by "dry skin care" or the use of 3% hexachlorophene soap. The administration of erythromycin in maximal doses (about 45 mg. per kg. in 6 divided doses daily for a week to all the infants) did prevent colonization and cleared the carrier state; infections did not then develop after discharge.

This prophylactic regimen was stopped 1 month after the epidemic ended. These workers, too, did not encounter erythromycin-resistant staphylococci, which is rather fortunate, since such conditions may be ideal for the occurrence and spread of such resistant strains (124, 125).

Klein and Rogers (126) observed an outbreak in which 20% of the infants developed skin infection after discharge from the nursery. They established surveillance and found that revision of the nursing technics produced only partial and temporary improvement for 1–2 months. They then introduced, in addition, the daily use of neomycin-gramicidin ointment in the nares of all infants and personnel and obtained a longer lasting improvement (at least 4 months). Donnison *et al.* (127) used a nasal cream containing neomycin plus chlorohexidine once daily to the anterior nares and hexachlorophene on the skin and thereby reduced significantly the number of nasal carriers of both penicillin-sensitive and -resistant staphylococci among the infants as compared with a control nursery. The staphylococcal carrier state of the mothers was not affected.

In another hospital situation, the inability to isolate carriers, patients and staff with infected lesions appeared to be a major factor in the failure to eliminate the phage type 80 staphylococcus (128). Considerable upheaval in hospital administrative practices failed to alter the incidence of the staphylococcal infections. The high carrier rates among staff and patients improved after the general use of neomycin cream in the anterior nares, but some nasal and skin carriers persisted in spite of this treatment, and the number of staphylococcal infections did not diminish significantly.

The Conference on Hospital Acquired Staphylococcal Infections held in Atlanta, Ga., in September 1958 condemned the systematic use of antibiotics prophylactically in newborn infants (115). The only possible exception, based on the experience of Shaffer *et al.* (122, 123) mentioned above, is for the persistent occurrence of infections with a single strain of high virulence which may be interrupted by the general use of an effective agent in full doses from birth until after the infants are discharged. The regimen is maintained until the epidemic strain is eliminated. This allows time to search for carriers and to correct defective technics. The antibiotics are thus employed only after careful evaluation of the particular situation, never for prolonged periods nor on a continuous basis. Ravenholt (129), at this conference, summed up the situation thus: "Sub-

stitution of antibiotic prophylaxis for adequate segregation and cleanliness is just as reprehensible in nurseries as it is in surgeries."

Interpretation of the results reported from the use of antibiotics in the prevention of staphylococcal infections in nurseries and in combating outbreaks of such infections is rendered very difficult by the pronounced fluctuation in the occurrence of such infections in nurseries where continuous observations have been made under different regimens. This is forcibly illustrated in epidemiologic studies of infections in nurseries recently reported by Gezon *et al.* (130).

PREMATURE INFANTS

It is generally assumed that premature infants are more susceptible to infection than normal full-term babies, especially during the first few days of life. In 1950, Clifford (131), reviewing the management of premature infants, concluded that infection was the most important factor in the higher than expected mortality of the small infants and believed that prophylactic administration of penicillin and streptomycin reduced this mortality. Later, Stoppelman (132), from a controlled study in the same nurseries, concluded that the improved mortality was a result of other features of the management. During the 8-month period of her study there was only 1 death from infection among 143 infants, although only one third of them received an antibiotic. Except for a reduction in streptococci by all treatments, she found no significant differences in the nasopharyngeal flora of untreated infants and of those treated from birth with full doses of oxytetracycline or with penicillin in combination with streptomycin or sulfadiazine. Cultures were sterile on the first day in 70%, but staphylococci predominated on the third day and thereafter. The emergence of pure cultures of this organism was noted only in those receiving antibiotics. Similar bacteriologic findings and failure to influence morbidity or mortality from infection by various antibiotic regimens was reported by Gialdroni-Grassi *et al.* (133) in a controlled study.

Snelling and Johnson (134), on the other hand, gave babies chlortetracycline, 50 mg. per kg. daily, and reported that morbidity decreased and rate of growth increased over those observed in the same nursery during a preceding period. Vyas (135) in India treated 50 premature infants with oxytetra-

cycline in doses of 25 mg. per kg. daily for 10 days, using no other drugs or vitamins; the mortality in this group was only 8% as compared with 40% in the previous year, and 90% in those weighing less than 4.5 lb. There was no fever, but some babies developed stomatitis, thrush or diarrhea; the diarrhea required stopping of the drug in 2 infants.

The opposing points of view regarding chemoprophylaxis in premature infants were brought out at a seminar of the American Academy of Pediatrics in 1956 (136). Alexander felt that infection was usually associated with other abnormalities and that premature infants should receive full therapeutic doses of the combination of chloramphenicol, erythromycin and sulfadiazine (100, 50 and 100 mg. per kg. per day) by mouth, omitting the erythromycin if the parenteral route were necessary. Levine, on the other hand, has adopted the policy of using antibiotics in prematures only for a specific indication, namely (1) premature rupture of membranes for 24–48 hours before delivery, (2) transfer from another nursery, and (3) evidence of infection.

The dangers of chemoprophylaxis which may lead to serious and fatal complications in premature babies must also be considered. Silverman *et al.* (137), in a controlled study, reported a high mortality, often associated with kernicterus, in such infants receiving sulfisoxazole in diethanolamine for the first 5 days of life. This has not occurred in studies with sulfadiazine, penicillin, streptomycin or tetracyclines (132–134). Several groups of workers have, however, reported on the so-called "gray syndrome" in prematures treated from birth with chloramphenicol in daily doses of 100 mg. per kg. or more. Such infants show a rapidly progressing picture of anorexia, lethargy, abdominal distention, respiratory distress followed by a shock-like state and a dusky-gray color (138–141). This has not occurred when doses of 50 mg. per kg. per day were used (141). Long-term use of moderate doses of chlortetracycline in premature infants has not produced any measurable untoward effects (142), nor have antibacterial agents other than sulfisoxazole-diethanolamine and chloramphenicol produced complications (132–134).

In reviewing the subject of neonatal mortality with reference to infection, Branton (143) differentiated the early deaths, attributable to infection in utero or during delivery, from the later ones, due to infection acquired from the environment. Deaths from some of the early acquired infections may be de-

layed by antimicrobials. In Branton's series, 38% of babies dying of all causes had received antimicrobials. Of 27 babies, including 20 prematures, whose death was clearly attributable to infection, 24 had received such treatment at some time during life, in 11 of them beginning after birth. Although not controlled, this study shows that antibiotics provided no real protection in many cases, since a rather large number of newborns developed infection, or had contracted infection before or during birth, which did not respond to therapy. When treatment is given, thorough bacteriologic studies of all potentially infected sites must precede the therapy.

STAPHYLOCOCCAL CARRIERS

The problem posed by carriers of coagulase-positive Staph. aureus with respect to the occurrence of infections and epidemics in nurseries and in postoperative wounds is an important and perplexing one. It is considered here mainly because of the importance attached by a number of workers to antibiotic prophylaxis and treatment of such carriers in attempts to eradicate the carrier state and thereby prevent the development of manifest staphylococcal infections in individuals and reduce their incidence in hospitals. A few recent and pertinent studies are therefore reviewed to permit some assessment of the present status of this problem.

Knight and Holzer (144) studied 516 strains of Staph. aureus isolated from carriers at Bellevue Hospital during 1953–1954 and found 56% of them resistant to penicillin, streptomycin and tetracyclines; more than 90% of these drug-resistant strains were of phage group III, which included the types most frequent in infections. In contrast, only 20% of 55 preserved strains that had been isolated from 1932 to 1938 were of group III, and these were predominantly susceptible to penicillin and streptomycin; all were highly sensitive to the tetracyclines and erythromycin. During 1953–1954, very few strains isolated from carriers at the time of hospitalization were of phage group III, but after treatment of the patients with tetracyclines, the latter types rapidly replaced the other strains. The same was true in patients treated with penicillin, but the changes occurred more slowly, whereas only a small proportion of those not treated with antibiotics acquired staphylococci of group III. From these and later studies, Knight *et al.* (145) believed that although the

drug treatment may influence the character of the staphylococci in the carriers and may temporarily suppress them, it apparently does not affect the tendency of the individual to become a carrier. The carrier state often coexists with infection and both are strongly influenced by host factors not related to treatment.

The nasal-carrier studies of Clarke (146) are of interest in this connection. He found that without antibiotic therapy a nose not carrying Staph. aureus was more liable to acquire penicillin-resistant staphylococci than one already carrying a penicillin-sensitive strain. Systemic treatment with antibiotics or sulfonamides increased the rate at which penicillin-sensitive staphylococci disappeared from the nose and thus increased the rate of spread of penicillin-resistant strains. Noses that had contained no staphylococci for a long time acquired them just as readily as those which had them until shortly before the swab was taken. However, the patients who had carried Staph. aureus for a long time lost them less readily than those who had carried them for only a short time. From observations in patients, Bernsten and McDermott (147) concluded that drug-resistant strains are not intrinsically more transmissible to adult patients than susceptible ones, but in patients treated with antibiotics there is an interference with the usual interspecies relations among the nasopharyngeal flora which thus increases the transmissibility of the drug-resistant strains to them.

Starkey (148) urged that attempts always be made in hospitals to identify the persistent carriers of large numbers of pyogenic staphylococci among operating-room and other key personnel and to control them through a hospital clinic. He felt that they should all receive active treatment appropriately chosen from among the following procedures: immunization with toxoid and/or autogenous vaccines; persistent treatment with a detergent nasal cream or spray containing nontoxic antistaphylococcal agents that are not generally used parenterally, such as tyrothricin, neomycin or bacitracin; regimens of washing with antiseptic soaps and detergents, and/or use of antiseptic creams (hexachlorophene, chlorhexidine, benzalkonium, etc.). It is not known, however, to what extent these measures would prove effective under controlled conditions.

The staphylococcal carrier problem was also considered in several papers presented at the National Conference on Hospital Acquired Staphylococcal Disease in Atlanta, Ga., in September 1958 (115). Williams (149) has traced several epidemics of operating-room sepsis to carriers among the hospital per-

sonnel, some of whom had septic lesions while others were apparently healthy. He considers the carriers to be the greatest problem because he found that 50–70% of the hospital staff carry Staph. aureus in their noses and 20–40% carry them on their skin; however, some of the carriers seem to be qualitatively different from others, or the staphylococci in some are more virulent. Thus, he was able to trace several outbreaks in maternity departments to single nurses who were carrying the epidemic strain, and he could also distinguish some patients who were actually or potentially dangerous on surgical wards. Healthy carriers, however, produced the greatest degree of aerial contamination.

Williams (149) found vigorous isolation of dangerous staphylococcus carriers and strict barrier nursing to be the best way of limiting cross-infection. Gould and Allen (150) treated nasal carriers with a tetracycline cream for a week and obtained a striking reduction in the number of staphylococcal infections. Later, Gould (151) applied a nasal cream of 0.5% neomycin and 1% chlorhexidine and succeeded in ridding most carriers of the organisms for a few weeks, but some did not respond to this treatment, even if their organisms were sensitive in vitro. Gillespie *et al.* (152) applied antibacterial creams to the nose of patients from the time of admission until they were discharged and achieved a drop in the number of positive cultures for staphylococci in wounds from 13 to 3%. However, experiences may vary from time to time even in the same hospital (130, 149). Thus, in 1 year at St. Bartholomew's Hospital, London, it was not possible to demonstrate that carriers among patients or personnel were the source of infections in patients; subsequently, in a study of 15 cases of postoperative sepsis, 7 were carriers of the same staphylococci in the nose or skin preoperatively. Some of these organisms may, of course, have been acquired in the hospital.

In the Central Laboratory at Colindale, a study of the strains from 94 epidemics over a period of 4 years showed that 18% of cultures taken from members of hospital staffs were of the local epidemic types. There was a striking difference between epidemics due to staphylococci of phage group I (including type 80/81), with about 25% staff carriers, and those of other phage groups, of which 3–13% of the staff were carriers. Apart from type 80 (or 80/81), which occurred in all sorts of hospitals, phage group I strains were infrequent outside of maternity hospitals. Williams (149) considered that the widespread nasal

carriage of epidemic strains among hospital staffs was not common enough to justify general nasal disinfection as a routine and that it is more likely to be relevant in maternity outbreaks than in surgical outbreaks, unless due to type 80.

Knight *et al.* (153) reported an experiment in a mental institution in which little in the way of antibiotics had been used and there were no erythromycin-resistant staphylococci. He treated a group of nasal carriers with oral erythromycin and they rapidly lost their staphylococci but gradually regained them within 2 weeks after the treatment was stopped. Five strains were found subsequently to be erythromycin-resistant. Untreated carriers showed no change during this time. The erythromycin-resistant organisms disappeared in a few weeks and most patients regained organisms of the pretreatment phage types. In another experiment, penicillin was given orally in large doses for 6 weeks to 16 persistent and 15 infrequent carriers. During treatment, the numbers of staphylococci counted in cultures dropped conspicuously, and 40% of swabs were negative, but the counts returned to pretreatment levels within 5 weeks. Sensitive organisms were replaced by penicillin-resistant ones during the treatment and then gradually disappeared, thus tending to re-establish the pretreatment distribution.

Lepper (154), discussing these findings, suggested that the rotation of drugs would not effectively eliminate resistant strains from hospital wards because they are slow in clearing after they accumulate in large numbers. He also pointed out that the use of combinations of drugs is dangerous and harmful if the population is already seeded with strains resistant to 1 of them; and even when 2 drugs are used to which staphylococci were originally sensitive, strains resistant to both drugs have appeared within 3 months. The use of many antibiotics at the same time, but singly in individual patients, might prove better; however, there are no data to bear that out. Lepper advocated minimizing the use of antibiotics and reserving some of them, like novobiocin, ristocetin and vancomycin, for serious staphylococcal infections, as the optimal procedures at present. The danger of widespread use of broad coverage with multiple antibiotics in determining the establishment and virulence of uncommon pathogens is well illustrated by the experience with Pseudomonas infections reported by Williams *et al.* (155) and is probably responsible in large measure for the increased incidence of infections with Proteus, Pseudomonas and Aerobacter (156, 157).

Shaffer (123) contends that most individuals who become asymptomatic carriers (through contact with patients) will stop carrying that particular strain when contact with the open infection stops. A few will continue to be carriers for weeks or months, and their disposition and treatment becomes a perplexing problem in the control of hospital infections. During 1 year he got good results by detecting and controlling carriers of strains pathogenic for newborns. Nasopharyngeal cultures were made before permitting duties on the maternity service and culture surveys were made monthly. Carriers were denied entry to nurseries and nurses were specially instructed if they had to be employed in the postpartum area. He was thus able to reduce infection with the epidemic strain to below 0.5%. In his experience, the only effective treatment for carriers has been prolonged freedom from contact with infected cases, and this was not always successful.

Colbeck (158) reported observations showing that patients who had positive skin cultures were 5 times as liable to sepsis as those with negative skin cultures. On the assumption that most skin carriers acquire infection from their nose, he investigated the possibility of controlling the nasal-carrier state prior to surgery by using a coarse plastic spray containing 1 mg. of neomycin per ml. in saline. This usually cleared the nose of staphylococci completely within a few days or markedly reduced the number. The patients were also instructed to use hexachlorophene soap for all washing, and after 2 days they were provided with fresh clothing and bedding. Pollution of the environment of even heavy excretors was usually rapidly eliminated or reduced by these measures.

It is of interest that the recommendations made in the summary report of the Conference (115) with regard to control of personnel carriers were concerned almost entirely with educational and administrative procedures. The extent of the latter varied with the presence or absence of epidemic spread of infection and whether or not the organism carried was of the epidemic type. As to the use of antibiotics for therapy or prophylaxis of carriers, the conference group was unable to recommend any of the procedures that had been used, but urged that they be further evaluated.

More recently, another group (128) expressed disappointment in its failure to reduce the incidence of cross-infections after considerable upheaval in hospital administrative practices. Although an initial drop in carrier rates among patients

and staff had been achieved with use of a nasal neomycin cream, some nasal and skin carriers persisted and the number of infections was not influenced. Inability to maintain adequate isolation of carriers was considered a major factor in the failure to eliminate the type 80 staphylococci.

A study of postoperative complications in patients undergoing elective surgery in a large tuberculosis hospital indicated that 34% of the patients yielded Staph. aureus from nasal cultures preoperatively (159, 160). Complications were more frequent and much more often due to infection, usually with organisms of the same type, in the nasal carriers of staphylococcus than in those with negative nasal cultures. Topical application of bacitracin-neomycin ointment resulted in negative cultures in 72% of treated patients, as compared with negative cultures in 23% of placebo-treated and 22% of untreated controls. Although the over-all effects on the postoperative complications were inconclusive, it is of interest that no complications were recorded in 12 patients in whom the treatment eliminated the staphylococci, whereas complications occurred in 5 of 7 patients in whom the treatment failed and nasal cultures continued to yield the organisms.

MONILIASIS

When the normal flora of the alimentary canal, or the mixed flora of a chronically infected respiratory tract, is markedly suppressed, yeasts and fungi may proliferate. In some patients, particularly in dehydrated and debilitated infants or other patients with severe chronic diseases, these organisms may cause infection of mucous membranes and skin and occasionally of the respiratory or urinary tract with or without blood-stream invasion. The organism most often found in such cases is Candida albicans. Two antibiotics, nystatin and amphotericin B, have considerable mycostatic effect and have been used successfully in the treatment of moniliasis. Satisfactory parenteral dosage forms of nystatin are not available; those of amphotericin are difficult to administer, and there is only very slight absorption of the oral forms of both agents. In general, the more active the antibacterial therapy in suppressing the normal bowel flora, the more likely are the yeastlike organisms to proliferate. Felisate *et al.* (161) were able experimentally to establish C. albicans infection with granulomatous lesions and hemorrhagic alveolitis

in the lungs of rabbits only when they gave the organisms endobronchially together with tetracycline; this could not be reproduced when chloramphenicol or penicillin plus streptomycin was used instead of the tetracycline.

Spaulding *et al.* (162) produced the greatest suppression of the bacterial flora of the lower bowel by oral administration of the combination of 3 Gm. of neomycin and 200 mg. of polymyxin B daily, but in 35 of 37 patients so treated this was accompanied by increased growth of various yeasts; 15% of these were C. albicans and 40% were nonpathogenic Saccharomyces. The growth of these yeasts could be suppressed by the additional administration of 3,000,000 units of nystatin daily. Other controlled studies on the effects of tetracycline given alone or with nystatin have shown that the increased growth of the yeasts in the feces (which accompanies tetracycline administration) can be reduced considerably by the addition of nystatin (163–165).

In the largest series, involving over 500 patients, Stone and Mersheimer (166) recorded side effects, nearly all mild, in 11.4% of patients receiving daily doses of 1 Gm. of tetracycline alone and in only 3.6% of those given 1,000,000 units of nystatin daily in addition; gastrointestinal side effects were about twice as frequent when tetracycline alone was used. Vaginal moniliasis occurred in 4 women on tetracycline alone and in none of those treated with the combination. Hewitt *et al.* (163), on the other hand, observed the same incidence of side effects from tetracycline given alone as when given with nystatin. There was a slight but not significant preponderance of gastrointestinal side effects from the former, but they could establish no relation between the large number of yeasts in the feces and these side effects. Staphylococcus aureus occurred in large numbers in both groups.

Lepper and Pearson (165), using twice the dose employed by Stone and Mersheimer (166), could culture Candida in the feces of 37.5% of patients treated with tetracycline alone and in only 12% of those receiving nystatin in addition, but some nystatin-sensitive strains appeared in spite of treatment with this drug. Streptococci and staphylococci increased in both groups; Pseudomonas was more frequent with the combination of drugs. Diarrhea developed in 4 of the patients treated with the combined drugs and in 2 of the 39 who got tetracycline alone. This effect was not related to any specific organisms, and there was no evidence of any beneficial clinical effect from the nystatin. Metzger *et al.* (164) described similar effects on the

fecal flora in a smaller group of cases and stressed particularly the overgrowth of enterococci and a resulting increase in the total bacterial counts in both groups. Side effects were minimal, and there was no relation between the flora and the objective or subjective findings in the patients.

The effect of amphotericin B in tetracycline-treated patients was also studied under controlled conditions by Lepper *et al.* (167). Candida albicans occurred seldom in this study; when present, large amounts of amphotericin were required to suppress these organisms, and failure to do so was not due to their resistance. On the other hand, Stough *et al.* (168), using amphotericin B and tetracycline in a 1:5 ratio for 1 week, obtained 81–93% reduction in overgrowth of Candida as a result of adding the amphotericin, and none were cultured from 21 of 76 patients under such treatment. There were no untoward systemic effects from the combined therapy and the amphotericin did not interfere with the absorption of tetracycline. Although clinical evidence of monilial infection was not observed in the tetracycline-treated patients, these authors consider it wise to prevent overgrowth of the organisms and therefore recommend the combined therapy.

Both tetracycline and hydrocortisone have potentiated monilial infection in mice and, when used simultaneously, appeared to exert independent effects (169). Suppression of normal bacterial coliforms by antibiotics permits overgrowth of monilia in vitro also (170).

From the point of view of preventing serious monilial infection, once C. albicans overgrowth occurs, the most important factor is the re-establishment of the normal bacterial flora, in the presence of which the yeasts do not seem to flourish (170). This is best accomplished by stopping the active antibacterial therapy, particularly tetracycline or multiple antibiotics, which is suppressing the common flora of the alimentary canal. On almost every occasion when confronted with marked overgrowth of Candida in sputum and feces (and in some instances even when heavy growth of C. albicans was obtained in the urine and the organisms have invaded the blood stream), simple discontinuance of antibiotic therapy and the taking of food, without resort to mycostatic agents, have resulted in fairly prompt and nearly complete clearing of these organisms from blood and urine. Often their numbers were so reduced that they could no longer be cultured from sputum or feces within 2 or 3 days (171). It should only rarely be necessary to resort to the use of mycostatic drugs, and then only when the infection for which

antibacterial drugs are being given is still active, severe and life-threatening and the latter drugs must therefore be continued.

VIRAL AND RICKETTSIAL DISEASES

Although all of the known rickettsias are moderately or highly susceptible to certain antibiotics, notably the tetracyclines and chloramphenicol, only organisms of the psittacosis-lymphogranuloma group among the viruses are susceptible. Some attempts have been made to prevent or control these infections.

Psittacosis (Ornithosis)

Meyer (172), in summarizing the control measures available against psittacosis, indicated that, with the aid of tetracycline drugs, immature parakeets could be mass-produced, freed from infection, distributed and sold in pet shops. The number of human infections acquired in the home would thus be reduced. Parenteral or oral therapy with tetracycline compounds, 30 mg. per kg. daily, has improved the health of parakeets, reduced mortality, prevented epizootics and reduced the hazard of infection of aviary personnel (173). It does not always eliminate the carrier state in every bird, but if treatment in aviaries is repeated at regular intervals, eventually the infection may be eradicated. Such treatment has failed to sterilize the virus-laden lesions of turkeys or to prevent acquisition of the disease by workers in processing plants or by those marketing infected turkeys (172). Davis and Watkins (174), on the other hand, have observed the natural transmission of ornithosis from infected to healthy turkey poults and found that chlortetracycline, 100 Gm. per ton of feed, prevents this spread. The use of 200 Gm. per ton prevents the mortality and the development of lesions in ornithosis-infected poults. Such poults remain susceptible to later reinoculation, whereas adult turkeys that recover from ornithosis develop antibodies and are resistant to subsequent challenge.

Scrub Typhus

The problems that may be involved in the chemoprophylaxis of rickettsial diseases may be surmised from studies on scrub typhus carried out in Malaya (175). In an initial field trial, chloramphenicol given during exposure to the endemic disease proved disappointing in that, although the clinical disease was

prevented during administration of the drug, typical scrub typhus developed about a week after the last dose. This showed that the antibiotic, which readily cures the well-established disease, failed to destroy the Rickettsia tsutsugamuchi. However, the organisms were prevented from multiplying and failed to develop resistance during the drug administration, since subsequent treatment, with full doses, of the disease that later developed, readily controlled the infection.

In another trial in which viable rickettsias were inoculated intradermally in volunteers and chloramphenicol was given during the ensuing 28 days, the characteristic primary cutaneous lesion did not appear while the drug was taken; but typical scrub typhus developed in nearly all a week after the drug was stopped. When administration of the drug was begun the seventh day after the inoculation and given only at 4-day intervals, it did protect nearly all of the volunteers provided the doses were large enough—at least 3 Gm. each. These observations indicated that prevention of the disease after a known exposure requires a delicate balance between infection and therapy, such that limited multiplication of the rickettsias is permitted and suppression by the antibiotic is incomplete. Obviously this type of prophylaxis can have only limited application.

INFECTIONS DURING CORTICOSTEROID ADMINISTRATION

Antibiotics have been widely used in attempts to prevent serious infections in patients receiving long-term therapy with cortisone and related steroids. The experience of Gibbs *et al.* (176) with such usage on a dermatologic ward is summarized in the table. Antibiotic prophylaxis of patients receiving steroids

Treatment Group	No. of Patients	No. of Infections	% Infected
All patients admitted	306	27	8.8
Neither steroids nor antibiotics	192	5	2.6
Antibiotics only	41	3	7.3
Steroids only	42	5	11.9
Steroids and prophylactic doses of antibiotics	31	14	45.1

did not decrease and, indeed, may have contributed to an increase of incidence of staphylococcal infections in their patients. An adverse effect of antibiotics and steroids on experimental monilial infection has also been demonstrated (169).

RADIATION AND INFECTION

Benacerraf (177) recently reviewed the role of irradiation on resistance to infection and the protective effect of antibiotics in irradiated animals. X-radiation, to be sure, is lethal for germ-free animals, but the dose required is larger in such animals and they survive lethal doses longer than conventional animals. In atomic-bomb casualties after the second week, there was evidence of massive infection in the internal organs, and in experimental animals there is evidence of generalized infection after x-radiation. In mice, the organisms recovered are generally those of the normal intestinal flora, notably E. coli, Paracolon, Proteus and Pseudomonas. Antibiotic therapy increased the survival time in mice, rats and dogs and may decrease the mortality in mice, in which streptomycin has proved effective for this purpose (178, 179). The toxicity of streptomycin does not seem to be enhanced by x-rays (179). Diarrhea in irradiated mice has been reduced by streptomycin or oxytetracycline, but not by penicillin and nonabsorbable sulfonamides. However, predictions of the value of prophylactic treatment after irradiation seem unwarranted on the basis of data now available on animals (179).

SUMMARY

This discussion has been concerned with the results of the application of chemoprophylaxis, under various conditions, against specific infections, and in certain specific situations of increased susceptibility to infections as they are encountered in general medical and pediatric practice. The results of similar applications of chemoprophylaxis to the prevention of infection in surgical and obstetric practice will be considered in a subsequent issue, which will also contain a general discussion and concluding summary.

Although no reports of very recent experience are available, there appears to be good evidence that fairly small doses of sulfonamides, particularly sulfadiazine, protect against menin-

gococcal infections and will eradicate the meningococcus carrier state; when given simultaneously to all persons in a closed community, they will promptly control epidemics of meningococcal infections. Single oral doses of penicillin have proved effective in preventing gonorrhea, if taken shortly after exposure, and continuous prophylaxis of prostitutes with monthly doses of benzathine penicillin probably maintains them noninfectious and free from gonorrhea and syphilis. Penicillin applied at birth will also prevent gonorrheal ophthalmia of the newborn and, if given to an infected mother before delivery, will prevent congenital syphilis in the offspring. A therapeutic dose will probably prevent syphilis in an individual exposed to an actively infected case, if given within 3 months of the contact. There is a danger of reduction in the effectiveness of such therapy in both diseases through the spread of strains of reduced sensitivity. Mass treatment with large doses of benzathine penicillin applied more or less simultaneously to all infected and exposed individuals of large infected populations, and repeated at proper intervals, gives promise of eradicating certain other treponematoses, such as endemic syphilis, yaws, bejel and pinta.

Sulfonamides, particularly sulfadiazine, and also the tetracyclines have been successful in the past in controlling outbreaks of bacillary dysentery. But increasing numbers of strains and species of Shigella are being encountered that are resistant to one or more of the antibacterial agents that were previously effective. The same is true of E. coli diarrhea of infants, but it is still possible to control localized outbreaks of this infection in a nursery or institution by simultaneous oral treatment of all of the infants and small children with 1 or more drugs, particularly neomycin or 1 of its related antibiotics (kanamycin, paromycin, safromycin) plus polymyxin B or colistin. Neomycin or a related antibiotic given orally is also effective in preventing or minimizing the symptoms of hepatic coma and permits administration of proteins and of chlorothiazide without relapse in most cases.

Chemoprophylaxis aimed at minimizing the symptoms and complications of minor nonspecific or acute viral respiratory infections (or given for the prevention of serious acute bacterial pneumonias as complications of such viral infections) has not proved successful, particularly in hospitals, and the same is true in patients with acute cardiac failure, coma from various causes or tracheotomy for respiratory paralysis. This failure has generally been due to the inhibition or eradication of the

common susceptible pathogens and their replacement by others that are resistant to the drugs used. Complicating infections occur in prophylactically treated patients as frequently as, or more often than, in untreated controls; however, whereas they are usually amenable to treatment in the latter, they are much more difficult to control in the former.

In patients with chronic bronchitis, and possibly other chronic nontuberculous bronchopulmonary infections, particularly mucoviscidosis, the continuous administration of a tetracycline has effectively reduced the number of acute exacerbations of pulmonary infections requiring bed care at home or in the hospital and the number of days away from normal activity. This is particularly true when exacerbations are due to infections by pneumococci or H. influenzae. Evidence is also accumulating that the serious and frequently fatal complications of primary tuberculosis in children under 3 years of age can be prevented by continuous administration of isoniazid to those who have recently developed a positive tuberculin reaction. Such treatment may also provide protection to tuberculin-negative individuals exposed for brief periods to heavily infected and contagious individuals.

The prevention or elimination of staphylococcal infections in nurseries and, secondarily, in the mothers and families of newborn infants probably depends more on efficient barrier-nursing technics and meticulous attention to factors designed to prevent cross-infection (particularly the exclusion of infected carriers among the personnel) than they do on chemoprophylaxis. Favorable effects have been obtained for limited periods during epidemic prevalence by the application of neomycin and/or bacitracin ointments to the anterior nares and the use of nonirritating antiseptic powders or solutions to the entire trunk of newborn infants and for skin care of personnel. However, these are likely to be effective in halting epidemics *only* if employed in conjunction with improvements in nursing technics and environmental sanitation and if applied simultaneously to all children in the nursery. The use of antibiotics should be discontinued soon after the epidemic is controlled in order to minimize the chances for establishment of resistant strains.

Routine use of antibacterial agents for the prevention of infection in premature babies has not been useful in reducing infection or mortality, nor in preventing implantation of drug-resistant virulent organisms prevalent in the environment. Such usage has been accompanied by unfortunate complications, in-

cluding high mortality, with frequent kernicterus from the use of sulfisoxazole (Gantrisin) in diethanolamine and with the so-called gray syndrome from chloramphenicol in doses of 100 mg. per kg. or more. When there is a high risk of infection, careful clinical and bacteriologic observations of infants, including prematures and their mothers, and selective treatment, based as far as feasible on the cultural data, are preferable.

The management of carriers of virulent staphylococci of a type that is producing disease in a hospital is difficult and complex. Infected carriers of such strains should certainly be excluded from nurseries and operating theaters and from contact with very sick and susceptible patients. Elimination of the carrier state is most effectively accomplished, if at all, by proper treatment of the infection and prolonged removal from contact with other infected patients.

Available data do not justify the routine use of nystatin or amphotericin in patients being treated with broad-coverage antibiotics.

Possible chemoprophylaxis of rickettsial infections was demonstrated by the use of chloramphenicol in scrub typhus; this agent or 1 of the tetracyclines, if given before clinical symptoms appear, must be administered in repeated courses after the exposure, with properly spaced drug-free intervals. This should prove effective following accidental or natural inoculation of any rickettsia. It is also now possible, by intensive treatment with chlortetracycline of all young parakeets in an aviary and repetition of treatment at intervals, to rid the aviary of psittacosis and thus prevent infections of those who handle or purchase the birds.

The use of antibiotics to prevent infection in individuals exposed to heavy doses of x-radiation or in patients receiving continuous treatment with corticosteroids has not proved useful or effective. Early clinical and bacteriologic detection and prompt, intensive and specifically directed therapy are more likely to provide the best results in these situations, as in most of the others that have been discussed.

REFERENCES

1. Finland, M.: *Chemoprophylaxis of Infectious Diseases: I. General Considerations and Application to Streptococcal Infections, Rheumatic Fever, Glomerulonephritis and Bacterial Endocarditis,* DISEASE-A-MONTH (Chicago: Year Book Publishers, Inc., December, 1959).

2. Kuhns, D. M., Nelson, C. T., Feldman, H. A., and Kuhn, L. R.: Prophylactic value of sulfadiazine in control of meningococcic meningitis, J.A.M.A. 123:335, Oct. 9, 1943.
3. Phair, J. J., and Schoenbach, E. B.: Dynamics of meningococcal infections and effect of chemotherapy, Am. J. Hyg. 40:318, November, 1944.
4. Cheever, F. S.: Chemoprophylaxis of Meningococcal Infections and of Bacillary Dysentery, in MacLeod, C. M. (ed.): *An Evaluation of Chemotherapeutic Agents* (New York: Columbia University Press, 1949), pp. 113–120.
5. Eagle, H., Gude, A. V., Beckman, G. E., Mast, G., Sapero, J. J., and Shindledecker, J. B.: Prevention of gonorrhea with penicillin tablets, J.A.M.A. 140:940, July 16, 1949.
6. Babione, R. W., Hedgecock, L. P., and Ray, J. P., Navy experience with oral use of penicillin as prophylaxis, U.S. Armed Forces M. J. 3:973, July, 1952.
7. White, C. B.: Reactions to penicillin given orally in mass prophylaxis, U.S. Armed Forces M. J. 4:1606, November, 1953.
8. Durel, P.: Prophylaxie des maladies vénériennes chez les prostitutes par la benzathine penicillin G, Rev. hyg. et méd. soc. 6:98, 1958.
9. Guthe, T.: Prevention of venereal infections, Bull. World Health Organ. 19:405, 1958.
10. Reyn, A., Korner, B., and Bentzon, M.: Effects of penicillin, streptomycin and tetracycline on N. gonorrhoeae isolated in 1944 and in 1957, Brit. J. Ven. Dis. 34:227, 1958.
11. Keetel, W. C., Scott, J. W., and Plass, E. D.: Evaluation of prophylactic penicillin administration to parturient women, Am. J. Obst. & Gynec. 58:335, August, 1949.
12. Watts, S. G., and Gleich, M. M.: Penicillin-silver nitrate prophylaxis against gonorrheal ophthalmia of the newborn: Preliminary report on use of penicillin and silver nitrate combined and silver nitrate alone, J.A.M.A. 143:635, June 17, 1950.
13. Davidson, H. H., Hill, J. H., and Eastman, N. J.: Penicillin in prophylaxis of ophthalmia neonatorum, J.A.M.A. 145:1052, Apr. 7, 1951.
14. Committee on Medico-Legal Problems: Review of status of state laws requiring use of a prophylactic in the eyes of newborn infants, J.A.M.A. 169:1950, Apr. 18, 1959.
15. Hollander, D. H., Turner, T. B., and Nell, E. E.: Effect of long continued subcurative doses of penicillin during incubation period of experimental syphilis, Bull. Johns Hopkins Hosp. 90:105, February, 1952.
16. Plotke, F., Eisenberg, H., Baker, A. N., and Laughlin, M. E.: Penicillin in abortive treatment of syphilis, J. Ven. Dis. Inform. 30:252, September, 1949.
17. Alexander, L. L., and Schoch, A. G.: Prevention of syphilis: Penicillin calcium in oil and white wax, U.S.P. bismuth ethylcamphorate and oxophenarsine hydrochloride in treatment, during incubation

stage, of persons exposed to syphilis, Arch. Dermat. & Syph. 59:1, January, 1949.
18. King, A. J.: Drugs in treatment of syphilis, Brit. M. J. 1:355, Feb. 7, and 431, Feb. 14, 1959.
19. Shaffer, L. W., and Courville, C. J.: Effectiveness of penicillin in prevention of congenital syphilis, A.M.A. Arch. Dermat. & Syph. 63:91, January, 1951.
20. Nelson, N. A., and Struve, V. R.: Prevention of congenital syphilis by treatment of syphilis in pregnancy, J.A.M.A. 161:869, June 30, 1956.
21. Guthe, T., Reynolds, F. W., Krog, P., and Willcox, R. R.: Mass treatment of treponemal diseases, with particular reference to syphilis and yaws, Brit. M. J. 1:594, Mar. 14, 1953.
22. Hardy, A. V., and Watt, J.: The acute diarrheal diseases, J.A.M.A. 124:1173, Apr. 22, 1944.
23. Hardy, A. V.: Studies of the acute diarrheal diseases: XVII. The sulfonamides in shigellosis, Pub. Health Rep. 61:857, June 14, 1946.
24. Scadding, J. C.: Sulphonamides in bacillary dysentery, Lancet 2:549, Nov. 3, 1945.
25. Hardy, A. V., and Halbert, S. P.: Studies of the acute diarrheal diseases: XX. Further observations of chemotherapy in shigellosis; The efficacy of streptomycin and sulfacarzole, Pub. Health Rep. 63:790, June 11, 1948.
26. Alexander, M. B., *et al.*: Streptomycin treatment of infantile diarrhea and vomiting: Conduct and results of clinical trial, J. Hyg. 50: 246, June, 1952.
27. Johnson, R., and Landsman, J. B.: Antibiotic treatment in dysentery, Scottish M. J. 2:383, October, 1957.
28. Katsura, S., Aoki, T., and Ogihara, K.: Erfahrungen über die Langzeitbehandlung mit kleinen antibiotikadosen bei Massenepidemien von bazillärer Dysenterie, München. med. Wchnschr. 101:1318, July 31, 1959.
29. Wheeler, W. E., and Wainerman, B.: Treatment and prevention of epidemic infantile diarrhea due to E. coli 0-111 by use of chloramphenicol and neomycin, Pediatrics 14:357, October, 1954.
30. Todd, R. M., and Hall, E. G.: Correlation of clinical and bacteriological findings in infantile gastroenteritis, Arch. Dis. Childhood 30:345, August, 1955.
31. Buttiaux, R., Nicolle, P., Le Minor, L., Le Minor, S., and Gaudier, B.: Epidemiological study of gastroenteritides due to Escherichia coli in a hospital service in the north of France, Arch. mal. appa. digest. 45:225, October, 1956.
32. Markiewicz, D.: Study of epidemic of infantile gastroenteritis due to O11-B4 at the Brussels Center of Puericulture and Pediatrics, Acta paediat. belg. 10:227, 1956.
33. Martineau, B., Raymond, R., and Jeliu, G.: Bacteriological and clinical study of gastroenteritis with enteropathogenic Escherichia coli O127:B8, Canad. M.A.J. 79:351, Sept. 1, 1958.

34. Kunin, C. M., Wilcox, C., Najarian, A., and Finland, M.: Susceptibility and cross-resistance of bacteria to four related antibiotics, kanamycin, paromomycin, neomycin and streptomycin, Proc. Soc. Exper. Biol. & Med. 99:312, December, 1958.
35. Hinton, N. A., and MacGregor, R. R.: Study of infections due to pathogenic serogroups of Escherichia coli, Canad. M.A.J. 79:359, Sept. 1, 1958.
36. Stulberg, C. S., Zuelzer, W. W., Nolke, A. C., and Thompson, A. L.: Escherichia coli O127:B8, a pathogenic strain causing infantile diarrhea: 1. Epidemiology and bacteriology of prolonged outbreak in premature nursery, A.M.A. Am. J. Dis. Child. 90:125, August, 1955.
37. Cooke, R. E. (Report of Council on Drugs): Current status of therapy of infantile diarrhea, J.A.M.A. 167:1243, July 5, 1958.
38. Phear, E. B., Ruebner, B., Sherlock, S., and Summerskill, W. H. J.: Methionine toxicity in liver disease and its prevention by chlortetracycline, Clin. Sc. 15:93, February, 1956.
39. Gyorgy, J., Stokes, J., Jr., Goldblatt, H., and Popper, H.: Antimicrobial agents in prevention of dietary hepatic injury (necrosis, cirrhosis) in rats, J. Exper. Med. 93:513, June, 1951.
40. Reynell, P. C.: Aureomycin in experimental liver failure, J. Path. & Bact. 66:47, July, 1953.
41. Dawson, A. M., McLaren, J., and Sherlock, S.: Neomycin in treatment of hepatic coma, Lancet 2:1263, Dec. 21, 1957.
42. Fast, B. B., Wolfe, S. J., Stormont, J. M., and Davidson, C. S.: Antibiotic therapy in management of hepatic coma, A.M.A. Arch. Int. Med. 101:467, February, 1958.
43. Faloon, W. W., and Fischer, C. J.: Clinical experience with use of neomycin in hepatic coma, A.M.A. Arch. Int. Med. 103:45, January, 1959.
44. Stormont, J. M., Mackie, J. E., and Davidson, C. S.: Observations on antibiotics in treatment of hepatic coma and on factors contributing to prognosis, New England J. Med. 259:1145, Dec. 11, 1958.
45. Mackie, J. E., Stormont, J. M., Hollister, R. M., and Davidson, C. S.: Production of impending coma by chlorothiazide and its prevention by antibiotics, New England J. Med. 259:1151, Dec. 11, 1958.
46. Summerskill, W. H. J.: Hepatic coma in liver failure and gastrointestinal haemorrhage treated with neomycin, Brit. M. J. 2:1322, Nov. 29, 1958.
47. Kunin, C. M., *et al.*: Absorption of orally administered neomycin and kanamycin, with special reference to patients with severe hepatic and renal disease, New England J. Med. 262:380, Feb. 25, 1960.
48. Last, P. M., and Sherlock, S.: Systemic absorption of orally administered neomycin in liver disease, New England J. Med. 262:385, Feb. 25, 1960.
49. Finland, M.: Antimicrobial treatment for viral and related infections: II. Antibiotic treatment of acute respiratory infections and influenza, New England J. Med. 247:557, Oct. 9, 1952.

50. Personnel of Naval Medical Research Unit No. 4: Prophylaxis of acute respiratory infections with oral penicillin or chlortetracycline, Antibiotics Annual, 1953–1954, pp. 123–136.
51. Haight, T. H., Kahn, F. H., and Ziegra, S. R.: Efficacy of erythromycin in treatment of acute respiratory infections, U.S. Armed Forces M. J. 5:1405, October, 1954.
52. Gehrand, H. C.: Experiences in prevention of upper respiratory infections in general pediatric practice, Antibiotics Annual, 1955–1956, pp. 364–373.
53. Lapin, J. H.: Incidence of allergic reactions to penicillin in infants and children, Ann. Allergy 13:169, Mar.-Apr., 1955.
54. Hardy, L. M., and Traisman, H. S.: Antibiotics and chemotherapeutic agents in treatment of uncomplicated respiratory infections in children, J. Pediat. 48:146, February, 1956.
55. Townsend, E. H., Jr.: Chemoprophylaxis during respiratory infections in a private pediatric practice, A.M.A. J. Dis. Child. 98:515, October, 1959 (abstract).
56. Gibel, H., and Litvak, A. M.: Sulfathiazole in treatment of measles and its complications, J. Pediat. 21:315, September, 1942.
57. Karelitz, S., King, H., Curtis, B., and Wechsel, M.: Use of Aureomycin and penicillin in treatment of rubella, Pediatrics 7:193, February, 1951.
58. Karelitz, S., Chang, C. C., and Matthews, Z. E.: Prophylaxis of bacterial complications of measles with benzethacil and aqueous procaine penicillin G, J. Pediat. 44:357, April, 1954.
59. Karelitz, H. D., Isenberg, H. D., Gittelson, S. B., and Stillerman, M.: Antibiotic prophylaxis of bacterial complications of measles, J. Pediat. 54:1, January, 1959.
60. Weinstein, L.: Failure of chemotherapy to prevent bacterial complications of measles, New England J. Med. 253:679, Oct. 20, 1955.
61. College of General Practitioners: *The Complications of Measles* (London: 1956); quoted in an editorial: Treatment of measles, Brit. M. J. 2:90, July 14, 1956.
62. Ritchie, J. M.: Antibiotics in small doses for the common cold, Lancet 1:618, Mar. 22, 1958.
63. Ritchie, J. M.: Control of the common cold, Lancet 2:699, Sept. 27, 1958.
64. Ritchie, J. M.: Control of the common cold by autogenous vaccine or by antibiotics, Antibiotics Annual, 1958–1959, pp. 174–177.
65. Bloomfield, A. L.: Some problems of the common cold, J.A.M.A. 144:287, Sept. 23, 1950.
66. Gohd, R. S.: The common cold, New England J. Med. 250:687, Apr. 22, and 722, Apr. 29, 1954.
67. Sulman, F. G.: Chloramphenicol and control of the common cold, Lancet 2:1335, Dec. 20, 1958.
68. Chancey, R. L., and Meikeljohn, G.: Treatment of influenza with erythromycin, U.S. Armed Forces M. J. 5:839, June, 1954.

69. Cronk, G. A., and Naumann, D. E.: Ilotycin (erythromycin) in treatment of A-prime influenza, New York J. Med. 54:373, Feb. 1, 1954.
70. Finke, W.: Chemoprophylaxis of Asian influenza for patients with chronic pulmonary disease, Antibiotics Annual, 1958–1959, pp. 178–187.
71. Walker, W. C., *et al.*: Respiratory complications of influenza, Lancet 1:449, Mar. 1, 1958.
72. Lepper, M. H., *et al.*: Effect of eight antibiotics used singly or in combinations on tracheal flora following tracheotomy in poliomyelitis, Antibiotics & Chemother. 4:829, August, 1954.
73. Weinstein, L., Chang, T. W., and Mercer, G.: Unpublished data cited on p. 290 by Weinstein, L.: Chemoprophylaxis of infection, Ann. Int. Med. 43:287, August, 1955.
74. Livingstone, J. B., Austen, F. K., and Kunz, L. J.: Study of intercurrent bacterial respiratory infections in bulbospinal poliomyelitis, New England J. Med. 257:861, Oct. 31, 1957.
75. Woolmer, R.: Management of the apnoeic patient with special reference to bulbar poliomyelitis and tetanus, Postgrad. M. J. 31:463, Sept. 1, 1955.
76. McVay, L. V., Jr., Sprunt, D. H., and Stern, T. N.: Antibiotic prophylaxis in chronic congestive failure, Am. J. M. Sc. 226:491, November, 1954.
77. Petersdorf, R. G., and Merchant, R. K.: Study of antibiotic prophylaxis in patients with acute heart failure, New England J. Med. 260: 565, Mar. 19, 1959.
78. Petersdorf, R. G., *et al.*: Study of antibiotic prophylaxis in unconscious patients, New England J. Med. 257:1001, Nov. 21, 1957.
79. Weinstein, L., Seltser, R., and Marrow, C. T., III: Treatment of pertussis with Aureomycin, chloramphenicol and Terramycin, J. Pediat. 39:549, November, 1951.
80. Finke, W.: Public health aspects and prevention of bronchopulmonary disease, J.A.M.A. 151:105, Jan. 10, 1953.
81. Finke, W.: Combined antibiotic-cortisone therapy in infectious asthma: Rationale of its early application, New York J. Med. 54: 2685, Oct. 1, 1954.
82. Finke, W.: Penicillin V, tetracycline and prednisone in prolonged antibiotic-steroid treatment of infectious asthma, Antibiotics Annual, 1957–1958, pp. 431–437.
83. Lewis-Faning, E., and Davies, W.: Controlled trial of continuous oral penicillin therapy in asthmatic children during five winter months, Acta Allergol. 13:67, 1959.
84. McVay, L. V., Jr., and Sprunt, D. H.: Antibiotic prophylaxis in chronic respiratory diseases, A.M.A. Arch. Int. Med. 92:833, December, 1953.
85. Helm, W. H., May, J. R., and Livingstone, J. L.: Long-term oxytetracycline (Terramycin) therapy in advanced chronic respiratory infections, Lancet 2:630, Sept. 25, 1954.

86. May, J. R., and Oswald, N. C.: Long-term chemotherapy in chronic bronchitis, Lancet 2:814, Oct. 20, 1956.
87. Edwards, G., *et al.*: Adult chronic bronchitis—the infective factor and its treatment, Brit. M. J. 2:259, Aug. 3, 1957.
88. Edwards, G., and Fear, E. C.: Adult chronic bronchitis—continuous antibiotic therapy, Brit. M. J. 2:1010, Oct. 25, 1958.
89. Kirkpatrick, G. S., and Oldham, P. D.: Sulphonamide prophylaxis in chronic bronchitis: Clinical trial, Brit. M. J. 2:385, Aug. 14, 1954.
90. Bissell, S. W.: New sulphonamides, Brit. M. J. 2:1400, Dec. 19, 1959 (correspondence).
91. Buchanan, J., *et al.*: Long-term prophylactic administration of tetracycline to chronic bronchitis, Lancet 2:719, Oct. 4, 1958.
92. Elmes, P. C., Fletcher, C. M., and Dutton, A. A. C.: Prophylactic use of oxytetracycline for exacerbation of chronic bronchitis, Brit. M. J. 2:1272, Nov. 30, 1957.
93. Subcommittee of the Antibiotics Clinical Trials (Nontuberculous) Committee of the Medical Research Council: Prolonged antibiotic treatment of bronchiectasis, Brit. M. J. 2:255, Aug. 3, 1957.
94. Murdoch, J. M.: Evaluation of continuous antibiotic therapy in chronic bronchitis, Brit. M. J. 2:1277, Dec. 12, 1959.
95. Dowling, H. F., Mellody, M., Lepper, M. H., and Jackson, G. G.: Bacteriologic studies of sputum in patients with chronic bronchitis and bronchiectasis: Results of continuous therapy with tetracycline, penicillin or oleandomycin-penicillin mixture, Am. Rev. Resp. Dis. 81:329, March, 1960.
96. Hallett, W. Y., Beall, G. N., and Kirby, W. M. M.: Chemoprophylaxis in chronic obstructive pulmonary emphysema. Twelve week study with erythromycin, Am. Rev. Resp. Dis. 80:716, November, 1959.
97. Francis, R. S., and Spicer, C. C.: Chemotherapy in chronic bronchitis: Influence of daily penicillin and tetracyclines on exacerbations and their cost, Brit. M. J. 1:297, Jan. 30, 1960.
98. Shwachman, H.: Progress in study of "mucoviscidosis" (pancreatic fibrosis), Pediatrics 7:153, February, 1951.
99. Bruyn, H. B.: Use of Aureomycin in treatment of congenital fibrocystic disease, Am. J. Med. 11:627, November, 1951 (abstract).
100. Stowens, D.: Aureomycin in treatment of fibrocystic disease of the pancreas, Pediatrics 8:60, July, 1951.
101. Lambert, H. P.: Chemoprophylaxis of tuberculosis, Am. Rev. Resp. Dis. 80:648, November, 1959.
102. Ferebee, S. H., and Palmer, C. M.: Prevention of experimental tuberculosis with isoniazid, Am. Rev. Tuberc. 73:1, January, 1956.
103. Palmer, C. M., Ferebee, S. H., and Hopwood, L.: Prevention of experimental tuberculosis with isoniazid: II. Effect of different dosage regimens, Am. Rev. Tuberc. 74:917, December, 1956.
104. Bartmann, K.: Isoniazid prophylaxis in exposed or minimally infected animals, Bull. Internat. Union against Tuberc. 29:214, July-Oct., 1959.

105. Lincoln, E. M.: Effect of antimicrobial therapy on prognosis of primary tuberculosis in childhood, Am. Rev. Tuberc. 69:682, May, 1954.
106. Debré, R.: Systemic treatment of primary tuberculosis, New England J. Med. 255:794, Oct. 25, 1956.
107. Ferebee, S. H., Mount, F. W., and Anastasiades, A. A.: Prophylactic effects of isoniazid on primary tuberculosis in children: Preliminary report; A United States Public Health Service Tuberculosis Prophylaxis Trial, Am. Rev. Tuberc. 76:942, December, 1957.
108. Zorini, A. O.: Antituberculous chemoprophylaxis with isoniazid: Preliminary note, Dis. Chest 33:1, January, 1958.
109. Robinson, A., Meyer, M., and Middlebrook, G.: Tuberculin hypersensitivity in tuberculous infants treated with isoniazid, New England J. Med. 252:983, June 9, 1955.
110. Frostad, S.: Segmental atelectasis in children with primary tuberculosis, Am. Rev. Tuberc. 79:597, May, 1959.
111. Ryder, J. B.: Segmental lesions in drug-treated primary tuberculosis in young children, Brit. M. J. 1:324, Feb. 9, 1957.
112. Ryder, J. B.: Chemotherapy in primary tuberculosis, Brit. M. J. 1: 882, Apr. 13, 1957 (correspondence).
113. Dormer, B. A., Harrison, I., Swart, J. A., and Vidor, S. R.: Prophylactic isoniazid protection of infants in a tuberculosis hospital, Lancet 2:902, Nov. 21, 1959.
114. Anwar, S., *et al.*: *Chemotherapy and Chemoprophylaxis in Tuberculosis Control: Report of a Study Group,* World Health Organization Tech. Rep. Ser. No. 141, 1957.
115. Burney, L. E., *et al.*: *Hospital Acquired Staphylococcal Disease* (Proc. Nat. Conf., U.S.P.H.S. Communicable Disease Center and National Academy of Science–National Research Council, Atlanta, Ga., October, 1958).
116. Shaffer, T. E., Sylvester, R. F., Baldwin, J. N., and Rheims, M. S.: Staphylococcal infections in newborn infants: II. Report of 19 epidemics caused by an identical strain of Staphylococcus pyogenes, Am. J. Pub. Health 47:990, August, 1957.
117. Wentworth, F. H.: Miller, A. L., and Wentworth, B. B.: Observations relative to nature and control of epidemic staphylococcal disease, Am. J. Pub. Health 48:287, March, 1958.
118. Simpson, K., Tozer, R., and Gillespie, W. A.: Prevention of staphylococcal sepsis in a maternity hospital by means of hexachlorophane, Brit. M. J. 1:315, Jan. 30, 1960.
119. Forfar, J. O., *et al.*: Staphylococcal infection in the newborn treated with erythromycin, Lancet 1:584, Mar. 19, 1955.
120. Forfar, J. O., Maccabe, A. F., Balf, C. L., Wright, H., and Gould, G. C.: Staphylococcal infection in the newborn, Lancet 1:1071, May 21, 1955.
121. Forfar, J. O., and Maccabe, A. F.: Erythromycin: A review, Antibiotica et chemother. 4:115, 1957.
122. Shaffer, T. E., Baldwin, J. N., Rheins, M. S., and Sylvester, R. F., Jr.: Staphylococcal infections in newborn infants: I. Study of epi-

demic among infants and nursing mothers, Pediatrics 18:750, November, 1956.
123. Shaffer, T. E.: Staphylococcal infection in Newborn Nurseries, in Burney *et al.* (115), pp. 60–68.
124. Lepper, M. H., *et al.*: Epidemiology of erythromycin-resistant staphylococci in a hospital population—effect on therapeutic activity of erythromycin, Antibiotics Annual, 1953–1954, pp. 308–313.
125. Lowbury, E. J. L.: Clinical problems of drug-resistant pathogens, Brit. M. Bull. 16:73, January, 1960.
126. Klein, J. O., and Rogers, E. F. H.: Use of nasal antibiotic cream during nursery outbreak of staphylococcal disease, New England J. Med. 260:1012, May 14, 1959.
127. Donnison, B., Gillespie, W. A., Simpson, K., and Tozer, R. C.: Spread of staphylococci from hospital to community, Lancet 1:552, Mar. 5, 1960 (letter to editor).
128. Williams, J. R. B., Talbot, E. C. S., and Maughan, E.: Hospital outbreak of crossinfection due to Staphylococcus pyogenes phage type 80, Brit. M. J. 1:1374, May 30, 1959.
129. Ravenholt, R. T.: Discussion of "Staphylococcal Infection in Newborn Nurseries," in Burney *et al.* (115), pp. 69–74.
130. Gezon, H. M., Rogers, K. D., Thompson, D. J., and Hatch, T. F.: Some controversial aspects in epidemiology of hospital nursery staphylococcal infections, Am. J. Pub. Health 50:473, April, 1960.
131. Clifford, S. H.: Prevention and control of infection in nurseries for premature infants, A.M.A. Am. J. Dis. Child. 79:372, February, 1950.
132. Stoppelman, M. R. H.: Effect of antibiotics on nasopharyngeal flora of premature infants, A.M.A. Am. J. Dis. Child. 88:339, September, 1954.
133. Gialdroni-Grassi, G., Pryles, C. V., and Finland, M.: Controlled study of use of prophylactic antibacterials in premature infants, Pediatrics 18:899, December, 1956.
134. Snelling, C. E., and Johnson, R.: Value of Aureomycin in preventing crossinfection in the Hospital for Sick Children, Canad. M.A.J. 66:6, July 1, 1952.
135. Vyas, K. J.: Oxytetracycline in premature infants, Indian M. J., March, 1957; reported in Foreign Letters, J.A.M.A. 164:1375, July 20, 1957.
136. Alexander, H.: Antibiotic therapy (discussion in Seminar on Premature and Newborn Infants, Am. Acad. Pediat. Oct. 6-7, 1956), Pediatrics 20:152, July, 1957.
137. Silverman, W. A., Anderson, D. H., Blanc, W. A., and Crozier, D. N.: Difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens, Pediatrics 18:614, October, 1956.
138. Kent, S. P., and Wideman, G. L.: Prophylactic antibiotic therapy in infants born after premature rupture of membranes, J.A.M.A. 171: 1199, Oct. 31, 1959.

139. Sutherland, J. M.: Fatal cardiovascular collapse in infants receiving large amounts of chloramphenicol, A.M.A. J. Dis. Child. 97:761, June, 1959.
140. Burns, L. E., Hodgman, J. E., and Cass, A. B.: Fatal circulatory collapse in premature infants receiving chloramphenicol, New England J. Med. 261:1318, Dec. 24, 1959.
141. Editorial: Toxicity of drugs in premature infants, New England J. Med. 261:1343, Dec. 24, 1959.
142. Hines, L. R.: Appraisal of effects of long-term chlortetracycline administration, Antibiotics & Chemother. 6:623, November, 1956.
143. Branton, L. N.: Neonatal mortality with special reference to infectious causes of death, Am. J. M. Sc. 238:760, December, 1959.
144. Knight, V., and Holzer, A. R.: Studies on staphylococci from hospital patients: I. Predominance of strains of group III phage patterns which are resistant to multiple antibiotics, J. Clin. Invest. 33:1190, September, 1954.
145. Knight, V., White, A. C., and Martin, M. P.: Effect of antimicrobial drugs on staphylococcal flora of hospital patients, Ann. Int. Med. 49:536, September, 1958.
146. Clarke, S. K. R.: Nasal carriage of Staphylococcus aureus, J. Path. & Bact. 73:253, 1957.
147. Bernsten, C. A., and McDermott, W.: Increased transmissibility of staphylococci to patients receiving an antimicrobial drug, New England J. Med. 262:637, Mar. 31, 1960.
148. Starkey, H.: Control of staphylococcal infections in hospitals, Canad. M.A.J. 75:371, Sept. 1, 1956.
149. Williams, R. E. O.: Investigations of Hospital-Acquired Staphylococcal Disease and Its Control in Great Britain, in Burney *et al.* (115), pp. 11–29.
150. Gould, J. C., and Allan, W. S. A.: Staphylococcus pyogenes cross-infection: Prevention by treatment of carriers, Lancet 2:988, Nov. 11, 1954.
151. Gould, J. C.: Effect of local antibiotic on nasal carriage of Staphylococcus aureus, J. Hyg. 53:379, September, 1955.
152. Gillespie, W. A., *et al.*: Staphylococcal cross-infection in surgery: Effects of some preventive measures, Lancet 2:781, Nov. 7, 1958.
153. Knight, V., White, A., and Hemmerly, T.: The Effect of Antibiotics on Staphylococci of Hospitalized Patients, in Burney *et al.* (115), pp. 39–54.
154. Lepper, M. H.: Discussion of "Antibiotic Resistance of Staphylococci," in Burney *et al.* (115), pp. 55–59.
155. Williams, R., Williams, E. D., and Hyanis, D. E.: Cross-infection with Pseudomonas pyocyanea, Lancet 1:376, Feb. 13, 1960.
156. Yow, E. M.: Clinical significance of rising incidence of infections due to gram-negative bacilli, Postgrad. Med. 17:413, May, 1955.
157. Finland, M., Jones, W. F., Jr., and Barnes, M. W.: Occurrence of serious bacterial infections since introduction of antibacterial agents, J.A.M.A. 170:2188, Aug. 29, 1959.

158. Colbeck, J. C.: The Use of the Laboratory in the Epidemiology of Staphylococcal Disease, in Burney *et al.* (115), pp. 123–133.
159. Weinstein, H. J.: Relation between nasal staphylococcal carrier state and incidence of postoperative complications, New England J. Med. 260:1303, June 25, 1959.
160. Weinstein, H. J.: Control of nasal staphylococcal carrier state, New England J. Med. 260:1308, June 25, 1959.
161. Felisati, D., Bastianini, L., and de Mitre, T.: Antibiotics and Candida albicans given by endobronchial route, Antibiotics & Chemother. 9:744, December, 1959.
162. Spaulding, E. H., Rao, N. V., Tyson, R., Zubrzycki, L., and Harris, M. J.: Antifungal action of nystatin on fecal flora during administration of neomycin-polymyxin, Antibiotics Annual, 1955–1956, pp. 681–689.
163. Hewitt, W. L., Finegold, S. M., and Sutter, V. L.: Incidence of side effects and changes in fecal microflora following administration of tetracycline and tetracycline-nystatin, Antibiotics Annual, 1955–1956, pp. 856–861.
164. Metzger, W. I., *et al.*: Comparative effects of tetracycline alone and in combination with nystatin on intestinal flora of man, Antibiotics Annual, 1956–1957, pp. 208–215.
165. Lepper, M. H., and Pearson, J. Z.: Study of effect of tetracycline plus nystatin on aerobic fecal flora as compared to tetracycline alone, Antibiotics Annual, 1956–1957, pp. 220–227.
166. Stone, M. L., and Mersheimer, W. L.: Comparison of side effects of tetracycline and tetracycline combined with nystatin: Preliminary report, Antibiotics Annual, 1955–1956, pp. 862–866.
167. Lepper, M. H., Spies, H. W., and Rubens, M.: Use of amphotericin to eliminate Candida from stool of infants treated with tetracycline, Antibiotics Annual, 1958–1959, pp. 672–676.
168. Stough, A. R., Groel, J. T., and Kroeger, W. H.: Amphotericin B, new antifungal agent for prophylaxis of antibiotic-induced moniliasis, Antibiotic Med. 6:653, November, 1959.
169. Henry, B., and Fahlberg, W. J.: Potentiating effect of hydrocortisone acetate and tetracycline on monilial infections in mice, Antibiotics & Chemother. 10:114, February, 1960.
170. Paine, T. F., Jr.: In vitro experiments with Monilia and Escherichia coli to explain moniliasis in patients receiving antibiotics, Antibiotics & Chemother. 2:653, December, 1952.
171. Finland, M.: Unpublished observations.
172. Meyer, K. F.: Psittacosis--Lymphogranuloma Venereum Group, in Rivers, T. M.: *Viral and Rickettsial Infections of Man* (2d ed.; Philadelphia: J. B. Lippincott Company, 1959).
173. Meyer, K. F., *et al.*: Chemotherapy, in Beaudette, F. R. (ed.): *Progress in Psittacosis Research and Control* (New Brunswick, N. J.: Rutgers University Press, 1958).
174. Davis, D. E., and Watkins, J. R.: Effect of chlortetracycline in im-

munological response of turkeys infected with ornithosis, J. Infect. Dis. 104:56, Jan.-Feb., 1959.
175. Smadel, J. E.: Influence of antibiotics on immunologic responses in scrub typhus, Am. J. Med. 17:246, August, 1954.
176. Gibbs, R. C., Biro, L., and Sulzberger, M. B.: Prophylactic administration of antibiotics in patients receiving steroids systemically, J.A.M.A. 172:11, Jan. 2, 1960.
177. Benacerraf, B.: Influence of irradiation on resistance to infection, Bact. Rev. 24:35, March, 1960.
178. Miller, C. P., Hammond, C. W., and Tompkins, M.: Treatment of postradiation infection with antibiotics: Experimental study in mice, J. Lab. & Clin. Med. 39:462, March, 1952.
179. Smith, W. W., *et al.*: Prophylactic antibiotic therapy on x-irradiated animals, Am. J. Physiol. 172:351, February, 1953.
180. Miller, D. L., McDonald, G. C., Williams, R. E. O., and Wilson, J. S.: A trial of bacterial vaccines for the common cold in the Royal Air Force, Lancet 1:358, 1960.

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